Exhibit B

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: *Wave 4 Cases*	

EXPERT REPORT OF NICOLE B. FLEISCHMANN, M.D.

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Gynecare Gynemesh PS/Prolift/Prolift +M

I have prepared this Expert Report in the matter of In re: Ethicon, Inc. Pelvic Repair System Products Liability Litigation, MDL No. 2327, currently pending in the United States District Court for the Southern District of West Virginia, before the Hon. Joseph R. Goodwin. My opinions set forth in this report are made to a reasonable degree of medical probability, and are based on information and knowledge I have acquired from my research and review of medical literature, personal experience in private practice, education, training, teaching, and discussion and interaction with other pelvic surgeons in professional activities and conferences. I reserve the right to amend this report or my opinions as I review additional information.

QUALIFICATIONS

I am a practicing urologist with subspecialty training in Female Pelvic Medicine and Reconstructive Surgery (FPMRS). I have board certification both in Urology and in FPMRS, a new board certification with the American Board of Urology (ABU) and the American Board of OB/GYN (ABOG). Following my graduation from medical school and my residencies in surgery and in urology, I completed a fellowship in Female Urology and Voiding Dysfunction at the New York University School of Medicine. Since my fellowship, I have had a busy clinical practice at Westchester Urological Associates, a division of Advanced Urology in White Plains, New York, where I treat almost exclusively women with urologic issues such as incontinence, pelvic organ prolapse, recurrent urinary tract infections, hematuria and kidney stones. In addition to my private practice at White Plains Hospital, I am very involved in the training of residents (Urology and Gynecology) and fellows through my responsibilities as the Associate

Fellowship Director of FPMRS and Associate Clinical Professor of Urology and Ob/Gyn at Albert Einstein College of Medicine in Bronx, NY. I run a clinic, didactic sessions and perform surgery at the teaching hospital once a week. My credentials are further set forth in my *curriculum vitae*, which is Exhibit A to this Report.

On a daily basis, I diagnose and treat women with pelvic organ prolapse (POP), a debilitating condition which affects millions of women around the world. I take great pleasure in working to eliminate this problem for women and improving their overall quality of life, through both surgical and non-surgical treatment. For at least two or three days of the week, I perform and train others to perform surgical procedures to correct pelvic organ prolapse. Currently, I perform vaginal procedures with native tissue and biologic grafts, robotic sacral colpopexy using Y-mesh as well as obliterative procedures. In addition, I perform anti-incontinence procedures such as TVT and TVT-O, autologous fascial slings and robotic Burch colposuspensions on a routine basis. Prior to 2012, the overwhelming majority of the procedures that I performed to treat POP were the Gynecare Prolift and Prolift +M (Gynecare/Ethicon, Somerville, NJ). Over the span of 5 years I performed over 500 procedures to implant Prolift, including at least 200 Prolift +M.

Based on Ethicon's records, I attended an Ethicon-sponsored Professional Education event for TVT in 2002 (and a Prolift preceptorship and proctorship in 2006 and 2007, respectively), but the bulk of my training on Prolift was during in my clinical practice.

MATERIALS I HAVE REVIEWED

In the course of preparing this report, I have reviewed numerous documents. I have examined the published literature on Gynemesh PS, Prolift and Prolift +M. I have reviewed

professional education materials produced by Ethicon, as well as the Instructions for Use (IFU) of these products and Prolift patient brochures. I have also read the medical society statements and statements issued by the Food and Drug Administration (FDA) regarding transvaginal mesh repair of pelvic organ prolapse. I have also read numerous company documents. A list of the materials I have reviewed in formulating my opinions accompanies this report and will be updated as I review more materials.

PELVIC ORGAN PROLAPSE

Vaginal or pelvic organ prolapse (POP), an anatomic support defect of the pelvic viscera, affects millions of women in the United States. According to the International Urogynecologic Association (IUGA), this condition refers to the bulging or herniation of one or more pelvic organs into or out of the vagina. The pelvic organs consist of the uterus, vagina, bowel and bladder. Pelvic organ prolapse occurs when the muscles, ligaments and fascia (a network of supporting tissue) that hold these organs in their correct positions become weakened. The term prolapse comes from the Latin term "prolabi" which means "to slip down." POP, when defined by symptoms, has a prevalence of 3-6% and up to 50% when based upon vaginal examination. The incidence of POP surgery ranges from 1.5 to 1.8 per 1,000 women years and peaks in women aged 60-69. (Barber, Maher, Int. Urogyn. J. 2013 Nov.; 24(11):1783-90). According to Nygard (JAMA 2008), 24% of women in the USA are affected by pelvic floor disorders, with 16% of women experiencing urinary incontinence, 3% of women experiencing pelvic organ prolapse and 9% of women experiencing fecal incontinence. The prevalence of these conditions increases significantly with age: 10% of women aged 20–39 years compared with 50% of women aged 80 years or older suffer from at least one of these disorders. Over 225,000 women

underwent prolapse operations in the USA in 1997, making this one of the most common indications for surgery in women. (Sung, V. et al., Am. J. Obstet. Gynecol. 2010 May; 2012).

Vaginal prolapse has a varied effect on pelvic organ function from patient to patient. Many asymptomatic women present with POP to gynecologists on routine exam and are told that they have the condition. Others present with uncomfortable symptoms such as urinary incontinence, voiding difficulties, defecatory dysfunction, recurrent urinary tract infections, dyspareunia and uncomfortable or even painful bulge symptoms. (Bradley, CS et al. Obstet Gynecol. 2008 May;111(5):1148-53.) Symptoms tend to get worse with increasing degree of prolapse, especially pelvic pressure, voiding and evacuation difficulties. (Ellerkmann RM et al., Am. J. Obstet. Gynecol. 2001 Dec;185(6):1332-7). In severe cases, POP can cause complete urinary retention and even kidney failure. (Dongol A, et al., Kathmandu Univ. Med. J. (KUMJ). 2013 Jan-Mar;11(41):71-4).

In addition to the compromise of pelvic organ function that is associated with pelvic organ prolapse, there can be significant impairment of quality of life. Women seeking treatment for pelvic organ prolapse have a higher prevalence of depressive symptoms compared to controls without prolapse. Within the group of women with prolapse, women with baseline depressive symptoms report a lower QOL with higher PFIQ scores than women without baseline depressive symptoms. PFIQ scores and depressive symptoms improve dramatically following surgery in cases. (Chiara Ghetti et al., Int. Urogyn. J. 2010 Jul; 21(7): 855–860). Furthermore, a deleterious effect on sexual function has also been reported. Impairment of sexual relations and duration of abstinence are strongly associated with worsening pelvic organ prolapse. (Ellerkmann 2001, Handa, 2004). Edenfield (2015) found that one quarter of otherwise sexually active women with pelvic organ prolapse would refrain from sexual activity because of prolapse

symptoms. (J. Sex. Med. Feb;12(2):416-23). In addition, the strong correlation between POP and urinary incontinence (UI) subjects this population of women to all of the quality life issues associated with the latter condition. Compared with continent individuals, patients with UI have higher levels of anxiety, lower quality of life scores, and poorer life satisfaction. (Melvile 2002 Am. J. Obstet. Gynecology). As a result, urinary incontinence has an adverse effect on patients' daily lives, which can be embarrassing, devastating in the more extreme cases, and can become a barrier for normal social function.

The etiology of POP is complex and multifactorial. Childbirth, specifically vaginal delivery, is the predominant risk factor. POP affects about one in three women who have had one or more children and may occur during or shortly after a pregnancy or, may take many years to develop. (Lieschen H. et al., J. Reprod. Med. 2010 Mar-Apr; 55(3-4): 93–98). Caesarian section has been shown to be protective against pelvic prolapse in several large population studies. (Durnea CM et al., Int. Urogyn. J. 2014 Nov.;25(11):1463-70). Other risk factors include genetics, aging, obesity, chronic cough/smoking history, heavy lifting, previous pelvic surgery such as hysterectomy, connective tissue disorders and chronic constipation. In short, POP is caused by anything that puts pressure on a woman's pelvic floor and weakens the fascial and muscular attachments which support the pelvic organs.

Pelvic organ prolapse can involve one or more defects in the pelvic support system which can be described on a pelvic exam. In his landmark article, John Delancey (1992) described the three levels of support of the vagina after hysterectomy. Through cadaveric dissection, he concluded that the upper third of the vagina (level I) is suspended from the pelvic sidewall by the cardinal and uterosacral ligaments. The middle third of the vagina (level II) attaches laterally to the arcus tendineus fascia pelvis (ATFP) and fascia of the levator ani muscles. The vagina's

lower third fuses with the perineal membrane, levator ani muscles, and perineal body (level III). This anatomic description helped to lay the groundwork for how female pelvic surgeons evaluate and treat pelvic organ prolapse. Upper or apical vaginal prolapse i.e. uterus, vaginal vault (post hysterectomy) is a deficiency of the deepest attachments of the uterus, cervix and/or the upper third of the vagina to the pelvic ligaments which support these structures. Anterior vaginal wall prolapse, also known as cystocele, is descent of the bladder, and proximal part of the urethra. Posterior vaginal wall prolapse or rectocele is a deficiency of the septum between the rectum and vagina. It is often associated with a perineal deficiency. The term enterocele refers to a condition where small bowel is herniating through a defect in the vaginal wall. It can present as an apical, posterior or rarely, an anterior wall prolapse and is the most common form of apical prolapse post hysterectomy.

Diagnosing and Measuring Prolapse

Diagnosing pelvic organ prolapse can be complex. In some cases, a woman presents to her provider with classic symptoms of pelvic pressure, feeling of something protruding out of her vagina often accompanied by urinary symptoms such as frequency, urgency and difficulty holding the urine. Although complaints of a bulge are associated with the presence of prolapse, it is only weakly correlated with prolapse stage, and does not predict the site of the prolapse. (Ellerkman, 2001). Sometimes the patient presents without awareness of her prolapse. She may have other complaints such as recurrent urinary tract infections and incomplete bladder emptying. Sometimes the initial presentation is incontinence only, either stress or urge. As prolapse advances, symptoms of stress incontinence tend to improve as the urethra "kinks" from loss bladder support. This is usually accompanied by a weakened urinary stream and incomplete emptying with a sensation of constant fullness. In extreme cases, she may complain of an

inability to urinate or having to manually reduce the prolapse in order to void. Bowel symptoms such as constipation, fecal urgency and incontinence are not uncommonly associated. (Jelovsek JE, Maher C, Barber MD, Pelvic organ prolapse, Lancet. 2007;369(9566):1027.)

Initial evaluation of a woman with pelvic floor defects always involves a thorough history. The medical history includes symptoms specific to prolapse, as well as urinary, defecatory, and sexual problems, which are often associated with POP. The physician is interested in how long she has noticed the problem and how severe it is, i.e. how much it affects her quality of life; family history - did her mother have POP suggesting there may be a genetic component; childbirth history; whether she is planning more children, etc. In the course of the interview, the physician should learn about the everyday life of the patient: what she does for a living, does she exercise regularly or perform heavy lifting activities, is she a smoker, what her personal life is like, especially with regards to sexual activity, as all this information can be helpful when diagnosing and formulating a treatment plan. In addition, the medical history should include a review of medical comorbidities that could impact whether the patient is a candidate for surgical treatment.

Screening questionnaires are helpful in patients with higher stages of prolapse. Some epidemiologic studies have used validated pelvic floor distress questionnaire the Pelvic Floor Distress Inventory (PFDI) and the Pelvic Floor Impact Questionnaire (PFIQ) to assess prolapse symptoms with good reproducibility. (Barber et al., Am. J. Obstet. Gynecol. 2001;185(6):1388.) Symptom assessment is important, since treatment is generally not indicated for asymptomatic POP. In addition, assessment of POP symptoms and their impact on a patient's quality of life helps patients and clinicians set treatment goals. (Hullfish KL, Bovbjerg VE, Steers WD, Am. J. Obstet. Gynecol. 2004;191(1):201.)

Physical examination is crucial to the diagnosis of POP. As with many other anatomic conditions in medicine, there is a growing need for a standardized, reliable and clear staging method. In order to diagnose POP and devise an individualized treatment plan, patients and doctors need to understand both the characterization and quantification of the problem. The original systems for prolapse staging were organ based, describing the contents of the vaginal bulge as in "cystocele" or "rectocele." The problem with this terminology is that it required the doctor to surmise what was behind the vaginal bulge which is not always possible. Therefore, a movement to describing the location of wall protrusion such as "anterior", "posterior" or "apical" prolapse is preferred.

In 1968, Baden and Walker developed the Baden-Walker halfway scoring system for prolapse classification. The extent of prolapse is recorded using a number (0 to 4) at each of six sites in the vagina. Two sites are located on the anterior, superior and posterior walls of the vagina, respectively. The six numbers are recorded as a measure of descent. The hymen (opening of the vagina) is used as a fixed anatomic reference point. Zero indicates a normal anatomic position for a site, whereas 4 represents maximum prolapse. Between these extremes, the intervening numbers grade descent using a halfway system. The examination is performed with the patient straining so that maximum descent is attained. The Baden-Walker system is still used today due to its relative ease to adopt. For example, a "grade 3 cystocele" refers to anterior vaginal wall descent halfway beyond the hymen during straining maneuvers.

Because the Baden-Walker system relies on the older description of pelvic organ prolapse (i.e. cystocele and rectocele) and because the system is not validated, most of the more current literature uses the Pelvic Organ Prolapse Quantification system (POP-Q), created in 1996 by the standardization subcommittee of the ICS in collaboration with AUGS and the SGS (Bump,

1996). The hymen acts as the fixed point of reference throughout the POPQ system. There are six defined points for measurement in the POPQ system – Aa, Ba, C, D, Ap, Bp and three others landmarks: GH, TVL, PB. Each is measured in centimeters above or proximal to the hymen (negative number) or centimeters below or distal to the hymen (positive number) with the plane of the hymen being defined as zero (0). The hymen was selected as the reference point rather the introitus because it is more precisely identified. The terminology avoids assigning a specific label, such as cystocele or rectocele, to the prolapsing part of the vagina, acknowledging that the actual organ(s) above the prolapse frequently cannot be determined by physical examination. Once the measurements are taken, the patients are assigned to the corresponding stage 0 through 4, with 4 being complete loss of vaginal support.

Overall the POPQ has been a reliable and reproducible system for measuring pelvic organ prolapse. It is the only accepted system for quantifying prolapse in medical research. The drawback is that it is cumbersome and difficult to learn, making it relatively impractical in everyday practice. In 2006, this system was only used clinically by about 40% of members of ICS and AUGS. (Auwad W, Freeman RM, Swift S., Is the pelvic organ prolapse quantification system (POPQ) being used? A survey of members of the International Continence Society (ICS) and the American Urogynecologic Society (AUGS), Int. Urogyn. J. Pelvic Floor Dysfunct. 2004;15:324–327). A follow up study by Pham (2011) showed increased adoption of the POP-Q system: of the 308 specialists polled, 76% reported using the POP-Q. Of the 24% not using the POP-Q, more than 50% stated that the POP-Q is "too time-consuming" or that their "colleagues do not use it." Regardless of which measurement system is used, the physician needs to quantify the degree of prolapse and the compartments affected in order to form a treatment plan for the patient.

In addition, pelvic floor musculature should be assessed to see if the patient is able to perform pelvic floor strengthening exercises on her own. Guidelines were published by the International Continence Society (2012) to assess pelvic floor musculature tone. Four conditions have been defined: normal pelvic floor muscles can voluntarily contract and relax, overactive pelvic floor muscles are muscles cannot relax, underactive pelvic floor muscles cannot voluntarily contract, and non-functioning pelvic floor muscles is when there is no noticeable pelvic floor muscle contraction.

Additional testing

In the course of evaluating the woman with POP, most physicians will perform a post void residual test (PVR) in which the amount of urine left behind after a woman urinates is measured either by sonogram or catheter drainage. A urinalysis and urine culture determines when a urinary tract infection is present or when there is the presence of blood in the urine, which may indicate another problem such as bladder cancer. When indicated, clinicians may ask patients to keep a voiding diary to log the amount they drink, how often they urinate and how many leakage episodes they have in a 24-hour period.

Urodynamic testing can be an extremely helpful tool in diagnosing incontinence conditions. It is a procedure by which the physician is able to demonstrate the exact cause of incontinence by reproducing the episode in a controlled setting. The test involves placing a small catheter in the bladder and another in the rectum or vagina. The catheter monitors pressure as the bladder fills with water. The physician is able to assess the capacity of the bladder, whether there are any involuntary bladder contractions during the filling process, whether the patient leaks with a cough and at what volume and pressure, and whether the voiding episode is normal and unobstructed.

It is especially important during a preoperative urodynamic evaluation to perform a cough or Valsalva test when the prolapse is reduced – either with vaginal speculum, pessary or manually, to diagnose the condition of occult stress incontinence. This refers to the situation where the woman has no complaints of stress incontinence because when the vagina is in the prolapsed state, there is no leakage. However, when her bladder is reduced to its normal anatomic position, such as would be the case after reconstructive surgery, she leaks urine. Such a positive test would necessitate a simultaneous anti-incontinence procedure to be performed with the prolapse procedure. This form of testing is only 75% predicative of postoperative stress incontinence. A study by Borstad et al., showed that 25% of women with no signs of preoperative stress incontinence on urodynamic testing had symptomatic stress incontinence after surgery. (Borstad et al., The risk of developing urinary stress incontinence after vaginal repair in continent women. Acta Obstet. Gynecol. Scand. 1989;68:545-49).

In some cases, the physician will look inside the bladder with cystoscopy to assess whether there are any abnormalities which could cause urine leakage such as a bladder stone or foreign body. Imaging is rarely necessary for the treatment of pelvic organ prolapse. For patients with significant bowel complaints such as constipation or fecal incontinence, the physician will sometimes order defecography. Pelvic or dynamic pelvic MRI can be useful in diagnosing the internal organs which are effected by prolapse. However, there are no standardized criteria for use of this modality for the diagnosis of POP and its role in affecting clinical outcomes is uncertain. (Broekhuis SR, Fütterer JJ, Barentsz JO, Vierhout ME, Kluivers KB, Int. Urogynecol J Pelvic Floor Dysfunct. 2009;20(6):721.)

Nonsurgical Treatment of POP

In patients with asymptomatic or low stage prolapse, or patients with significant medical comorbidities, nonsurgical management should be recommended. This consists of watchful waiting, pelvic floor exercises with or without pelvic floor muscle therapy (PFMT) and intravaginal pessary. Expectant management is a reasonable option for any woman who is coping well with her symptoms and does not want treatment. So long as she is not showing signs of urinary retention which may lead to further deleterious issues with her urinary tract, there is no harm in waiting. Women who choose this approach must be vigilant about controlling chronic constipation, avoid heavy lifting or weight gain which could worsen the accelerate the disease process.

Pelvic floor exercises, when done properly (which may require the help of a physical therapist) have been shown to be helpful in the treatment of stage 1 – 3 prolapse. (Braekken IH, Majida M, Engh ME, Can pelvic floor muscle training reverse pelvic organ prolapse and reduce prolapse symptoms? An assessor-blinded, randomized, controlled trial, Am. J. Obstet. Gynecol. 2010; 203(2):170.e1). A multicenter randomized controlled study by Hagen et al. (Lancet, 2014) showed at least a short term benefit of PFMT in improving prolapse symptoms. However, prospective randomized trials have found no evidence to indicate that improvement of pelvic floor muscle tone leads to regression of pelvic organ prolapse. (Hagen 2011, Cochrane Database).

Vaginal support devices or pessaries are another mainstay of nonsurgical management of POP. These are variably shaped devices which can be inserted to hold up the bladder, uterus and vagina. Today, most pessaries are made of medical grade silicone and are ring type with or without central support, Gellhorn and donut shaped. Pessaries are used in daily practice by more

than 86% of gynecologists and 98% of urogynecologists. (Atnip SD., Pessary use and management for pelvic organ prolapse, Obstet. Gynecol. Clin. North Am. 2009;36(3):541–563.) Pessary use has few contraindications: lack of patient's ability to comply with follow-up and instructions (eg, dementia), vaginal fistulas, uterovaginal erosions, and undiagnosed uterovaginal bleeding. Vaginal erosions are indications for temporary pessary removal and treatment with topical estrogen.

Common side effects of pessary use include vaginal erosions and discharge. Vaginal odor and discharge are common. Vaginal erosions are reported in 3 to 24 percent of women using pessaries. (Powers K., Pessary use in advanced pelvic organ prolapse, Int. Urogyn. J. Pelvic Floor Dysfunct. 2006;17(2):160). Other common side effects include de novo (occult) stress urinary incontinence, interference with sexual intercourse, and difficulty with bowel movements. Urinary tract infections have been reported in up to 13 percent of pessary users and bacterial vaginosis in up to 32 percent. (Alnaif, B. et al., Bacterial vaginosis increases in pessary users, Int. Urogynecol. J. Pelvic Floor Dysfunct. 2000;11(4):219.). Furthermore, variations in patient anatomy may dictate the success of a pessary trial. A short vaginal length (<6 cm) and wide vaginal introitus (> 4 fingerbreadths) is associated for a poor ability to retain a pessary. (Clemons JL et al., Risk factors associated with an unsuccessful pessary fitting trial in women with pelvic organ prolapse, J. Obstet. Gynecol. 2004;190(2):345.) Other factors such as coexisting SUI and previous reconstructive surgery including hysterectomy make pessary fitting more difficult. (Nguyen JN, Jones CRJ, Wound Ostomy Continence Nurs. 2005;32(4):255.)

In general practice, pessary use seems safe but is not a viable option for many women, especially those who are sexually active and cannot manage the device on their own. The majority of patients need to come to the doctor every 3 months for a pessary cleaning and

vaginal wall check. In this way, they may have avoided surgery, but they suffer from a chronic condition which will never be cured, only managed. Furthermore, many patients who choose pessary in their early years find that after some time, they are unable to continue the therapy secondary to vaginal bleeding and erosions. In the patients who can be fit with a pessary, approximately 40 percent of women discontinue pessary use within one to two years. (Clemons JL, et al., Patient characteristics that are associated with continued pessary use versus surgery after 1 year. Am J Obstet Gynecol. 2004;191(1):159). Now, they are faced with a surgical procedure as an older person with likely more comorbidities than if they had opted for surgery in their healthier years. Lastly, although pessary neglect is a rare occurrence, it can lead to serious complications. Devices which have been left in unnoticed secondary to noncompliance may require surgical removal and can become embedded in surrounding tissues causing bladder and bowel perforations and fistulas. (Nallendran V. et al., Neglected vaginal ring pessary, J. Obstet. Gynaecol. 2006;26:274-5.)

Surgical Treatment of POP

Due to the relative ineffectiveness of conservative therapy for symptomatic POP, many women will choose to have surgical correction. The two options for surgery are reconstructive and obliterative. The goal of reconstructive surgery is to restore normal pelvic anatomy, including bladder and bowel function, without compromising sexual function in sexually active women. The goal of obliterative surgery is the same with the exception of sexual function preservation as this is generally performed in older women. Reconstructive surgery, which is the majority of pelvic floor surgery, often involves repair of multiple anatomic sites of prolapse (apical, anterior, and/or posterior), as with higher grades of prolapse, it is more likely that more

than one compartment is involved. (Rooney K. et al., Advanced anterior vaginal wall prolapse is highly correlated with apical prolapse, Am. J. Obstet. Gynecol. 2006;195(6):1837). Repair of each prolapse site and how to best perform a combined reconstruction, including repair of coexisting incontinence, must be considered when choosing an overall surgical approach. Surgical considerations are the route of the procedure: Vaginal or abdominal (open, laparoscopic or robotic), use of graft augmentation, need for anti-incontinence procedure and need for concomitant hysterectomy. The choice of a primary surgical procedure depends upon a variety of considerations, including the anatomic site of prolapse, presence incontinence, patient health status, previous surgical history and patient and surgeon preferences.

Anterior colporrahphy

Anterior colporrhaphy (also referred to as anterior repair or native tissue repair), which can be performed under general or regional anesthesia, usually involves some degree of excision and/or plication of redundant anterior vaginal wall mucosa (epithelium). In the classic procedure, an incision is made along the center of the front wall of the vagina starting proximal to the bladder neck and finishing at the cervix or apex of the vagina. The vaginal epithelium is dissected from the underlying supportive fascial layer. The weakened fascia is then plicated in the midline using absorbable stitches (Vicryl). The vaginal wall which was involved in the dissection is usually trimmed off at the end and closed with running or interrupted absorbable suture. At the end, a cystoscopy is performed to confirm bladder and ureteral integrity. This procedure is often combined with other procedures such as vaginal hysterectomy, posterior colporrhaphy, sling surgery and vaginal apical suspensions.

The primary drawback of the anterior colporrhaphy is a relatively high risk of recurrent prolapse. The reported recurrence of anterior vaginal prolapse after anterior colporrhaphy alone

is over 30%. (Weber AM, Walters ME, Anterior vaginal prolapse: review of anatomy and techniques of surgical repair. Obstet. Gynecol. 1997). Limitations of this repair arise from the principle that one is simply plicating already attenuated native tissue. It is thought that the tissues of women with prolapse have a reduced amount of good quality collagen making them inherently weak. (Jackson SR, et al., Changes in metabolism of collagen in genitourinary prolapse, Lancet 1996 June 15; 347 (9016):1658-61).

A randomized study of three different anterior colporrhaphy techniques by Weber et al. compared standard anterior colporrhaphy versus ultralateral anterior colporrhaphy with muscle plication, versus standard anterior colporrhaphy plus absorbable mesh (polyglactin 910 mesh). (Weber A. et al., Anterior colporrhaphy: a randomized trial of 3 surgical techniques. Am. J. Obstet. Gynecol. 2001). Over 50% of the women enrolled had stage III or greater anterior vaginal wall prolapse. At 1 year, the percentages of satisfactory or optimal anatomic outcome were relatively low: 10 or 33 (30%) for the standard colporrhaphy group, versus 11 of 24 (46%) for the ultralateral colporrhaphy, versus 11 of 26 (42%) for the standard plus mesh group. This adds to the data reflecting the lack of success of anterior colporrhaphy alone for anterior compartment defect.

The potential complications of anterior colporrhaphy include:

- Hemorrhage
- Bladder, urethral, or ureteral injury
- Hematoma
- Wound infection or dehiscence
- Vaginal pain or dyspareunia
- Urinary tract infection

- De novo or worsening detrusor overactivity
- Urinary retention
- Urogenital fistula
- Urethral diverticulum

(Deng D. et al., Anterior Compartment, in Vaginal Surgery for Incontinence and Prolapse, Zimmern 2006.)

Dyspareunia and pain are known complications from an anterior colporrhaphy and a Kelly plication. Kelly plication is a procedure for stress urinary incontinence where the tissue under the bladder neck is plicated to form a supportive shelf. (Francis WJ, Jeffcoate TN. Dyspareunia following vaginal operations. J. Obstet. Gynaecol. Br. Commonw. 1961 Feb; 68:1-10; Sohbati S. et al., Comparison between the Transobturator Tape Procedure and Anterior Colporrhaphy with the Kelly plication in the Treatment of Stress Urinary Incontinence: a Randomized Clinical Trial, Nephrol. Urol. Mon. 2015 September; 7(5).) In this series of 60 patients, dyspareunia persisted in 10% of the anterior colporrhaphy and Kelly plication group and none of the transobturator sling group. Weber et al. evaluated 81 women after anterior colporrhaphy, posterior colporrhaphy, and/or vaginal vault suspension and found a 19% (14/75) de novo dyspareunia rate.

Posterior colporrhaphy

A posterior compartment defect, also known as a rectocele, arises from either a weakness or tear in the tissue of the rectovaginal septum or a detachment of the septum from the perineal body, usually related to vaginal delivery. In order to repair the defect, the surgeon has to plicate or tighten the tissues of the septum (posterior colporrhaphy) and reattach the repaired septum to

the perineal body (perineorrhaphy). The procedure is often performed in conjunction with an anterior repair and may also be accompanied by hysterectomy and/or apical prolapse repair (see below).

The complications of posterior colporraphy are similar to anterior colporraphy. The most common complication is dyspareunia. The tightening of the vaginal tissues can cause a narrowing of the lumen of the vagina as well as scar tissue formation which can result in discomfort with relations after the procedure. In some cases, the discomfort can persist causing chronic dyspareunia. Pain with intercourse after posterior repair was first described in the literature by Francis and Jeffcoate (J. Obst. & Gyn. 1961), who attributed a 50% rate of dyspareunia to this procedure. Over the years, surgeons have developed techniques to decrease the rate by not overtightening the introitus, not performing levatoplasty or performing a "site specific" technique. (Brandner, SJ, Sex. Med. (2011); Porter WE, Steele A., Walsh P., Kohli N., Karram M., Am. J. Obstet. Gynecol. 1999 Dec; 181(6):1353-8; discussion 1358-9.) Even with these changes, authors have reported a 16-17% rate of dyspareunia following posterior repair and perineonorraphy. (Abramov, Y., Site-specific rectocele repair compared with standard posterior colporrhaphy, Obstet. Gynecol. (2005 Feb); 105(2):314-8.). Weber et al, 2000 found that those who had posterior colporrhaphy the rate of de novo dyspareunia was 26% (14/53), and for those who had Burch and posterior colporrhaphy the rate rose to 38% (8/21). Although posterior colporrhaphy with levator plication has been associated with an increased rate of dyspareunia, only 1 of the 15 patients who developed postoperative dyspareunia had levator plication.

Lowman et al. (2008) summarized postoperative dyspareunia for different prolapse procedures in the following table.

Dyspareunia rates	ASC N=224 (148) Handa et al	SSLF N=287 (106) Maher et al	Uterosacral suspension N=110 (34) Silva et al	Anterior posterior repair N =165 (81) Weber et al	Prolift N =129 (57)
Baseline (preop)	40.5 (60/148)	Unknown	20.6 (7/34)	8.0 (6/81)	36.8 (21/57)
De novo (postop)	14.5 (11/76)	36.1 (22/61)	25.9 (7/27)	19.0 (14/75)	16.7 (6/36)

Apical repair – Vaginal approach

Apical prolapse refers to the downward displacement of the vaginal apex, either the uterus and cervix or, in women who have undergone subtotal or total hysterectomy, the cervix or vaginal cuff. Support of the vaginal apex is primarily derived from the integrity of the uterosacral and cardinal ligaments in what Delancey referred to as level 1 support of the vagina. It is rare to find isolated apical prolapse or isolated prolapse of the anterior or posterior vaginal walls, since the defects in the connective tissue and muscle typically affect the entire support system. Most cases of symptomatic prolapse (stage 3 and above) have an apical component even if the obvious presenting defect is a cystocele or anterior compartment defect. For this reason, an anterior/posterior native tissue repair (level 2 repair) may be adequate for small relatively asymptomatic defects (stage 2 and below) but as the prolapse worsens, attention must be paid to

the top of the vagina (Shull BL, Pelvic organ prolapse. Am. J. Obstet. Gynecol. 1999;181(1):6-11).

Transvaginal apical repair benefits women who do not want the risk associated with abdominal procedures. Transvaginal surgery is performed in 80 to 90 percent of prolapse surgeries in the United States. (Boyles SH, et al., Procedures for pelvic organ prolapse in the United States, 1979-1997. Am. J. Obstet. Gynecol. 2003;188(1):108; Maher C, Feiner B, Baessler K, Christmann-Schmid C, Haya N, Brown. Surgery for women with apical vaginal prolapse, Cochrane Database Syst. Rev. 2016 Oct 1). This may be secondary to the minimally invasive nature of vaginal surgery and the ease of addressing the anterior and posterior compartments at the time of other vaginal surgery (e.g. vaginal hysterectomy). There are two primary modes of vaginal suspension described in the literature - sacrospinous ligament fixation (SSLF) and uterosacral ligament fixation (USLF).

Sacrospinous ligament fixation (SSLF)

The sacrospinous ligament is palpated just medial to the ischial spine in the female pelvis. It is a uniformly strong band of tissue in all women making it an ideal point of fixation of the upper vagina. The procedure is usually performed unilaterally (on the right side) but can be done bilaterally if there is ample vaginal tissue. In the classic procedure, a midline incision is made extending towards the apex/cervix in the posterior vaginal wall. The pararectal space is bluntly dissected to reach the sacrospinous ligament. A long right angle retractor (eg, Briesky-Navratril) is placed on the ischial spine to protect the pudendal neurovascular bundle and two others are used to retract the bladder superiorly and the rectum medially. A Deschamps needle driver is used to place a permanent suture (Prolene or Ethabond) 2 cm medial to the ischial spine

to avoid the pudendal neurovascular complex. Alternatively, some surgeons use a Capio needle suture capturing device (Boston Scientific, Natick, MA) to pass the suture through the ligament. If the sacrospinous ligament is attenuated or if the vagina is foreshortened and the apex cannot reach the sacrospinous ligament, the sutures can be placed through the iliococcygeus muscle. After suture placement, an anterior/posterior repair is performed (if necessary) and finally, the sutures to the ligament complex are placed through the muscularis on the undersurface of the posterior vaginal epithelium and tied. (Karram, MM, Walters, MD, Surgical treatment of vaginal vault prolapse and enterocele, in: Urogynecology and Reconstructive Pelvic Surgery, 3d ed., Walters, MD, Karram, MM (Eds), Mosby Elsevier, Philadelphia 2007).

Infectious complications are the most common type of adverse event with SSLF, and are generally mild (eg, cystitis). Organ injury complications involving ureter and bladder are infrequent but have been reported. Enterotomy and postoperative bowel complications are also rare. (Sze EH, Karram MM, Transvaginal repair of vault prolapse: a review, Obstet. Gynecol. 1997). Hemorrhage during SSLF is most commonly due to laceration of the inferior gluteal or pudendal vessels. (Barksdale PA, Elkins TE, Sanders CK, Jaramillo FE, Gasser RF, An anatomic approach to pelvic hemorrhage during sacrospinous ligament fixation of the vaginal vault, Obstet Gynecol. 1998). Postoperative pain or nerve dysfunction is likely due to injury to the branches of the sciatic nerve that cross the sacrospinous ligament. A large review by Beer et al. Eur J Obstet Gynecol Reprod Biol. 2005;119(2):144., which looked at over 2000 cases of SSLF, found the most common complications to be:

- Cystitis – 4.5 percent
- Fever, secondary wound healing, abscess, or septicemia – 4.1 percent
- Ureteral kinking– 2.9 percent

- Pain (unclassified, gluteal, or bladder) – 2.0 percent
- Hemorrhage/blood transfusion – 1.9 percent
- Nerve damage (eg, sciatic nerve) – 1.8 percent
- Injury to pelvic organs – 0.8 percent
- Pelvic or vaginal vault hematoma – 0.4 percent

There are some studies which address the effect of SSLF on sexual function. In the Maher Cochrane Review (2013), the rate of dyspareunia was 36 percent in pooled data from three randomized trials in which SSLS was compared with abdominal sacral colpopexy. Maher et al. report a dyspareunia rate of 10% in their matched-pairs study of sacrospinous fixation and ilioccygeal fixation. Ozcan, U et al. (1999) reported dyspareunia in 9.2% of patients. Richter and Dargent (1986) report a normal sexual life in 63% of their patients and 12 patients (13%) with vaginal stenosis postoperatively. Lovatsis and Drutz (2002) report eight cases of de novo dyspareunia among 293 patients (3.2%). In a recent prospective randomized trial of 374 women comparing quality of life and sexual function measures in two different types of transvaginal suspension procedures, the authors concluded that de novo dyspareunia occurrs in 5% and 10% by 12 and 24 months, respectively. Lukacz ES et al., Quality of Life and Sexual Function 2 Years After Vaginal Surgery for Prolapse, Obstet Gynecol. 2016 Jun;127(6):1071-9.

Nerve pain is a recognized outcome of SSLF. Buttock or tailbone pain, which may be due to involvement of peripheral nervous branches or to the tension on the ligament, occurs in around 6–14% of patients after SSLF. (Alevizon SJ, Finan MA. Sacrospinous colpopexy: management of postoperative pudendal nerve entrapment. Obstet Gynecol. 1996). The majority of cases of postoperative buttock pain resolve spontaneously or with medical management,

although in one report 3 of 18 patients with postoperative pain subsequently had chronic pain. (Lovatsis D, Drutz HP, Safety and efficacy of sacrospinous vault suspension. Int. Urogyn. J. Pelvic Floor Dysfunct. 2002). Persistent pelvic and perineal pain should raise suspicion of potential pudendal nerve entrapment.

Uterosacral ligament fixation (USLF)

Another option for transvaginal suspension of the vaginal apex is to use the band of dense tissue which arises from the uterus/cervix and attached to the anterior part of the sacrum. Uterosacral ligament fixation (USF) as described by Shull (2000) requires a concomitant vaginal hysterectomy (or previous hysterectomy) and is an intraperitoneal procedure. After the hysterectomy is performed, the bowel is packed away with a moistened laparotomy sponge and a retractor is placed to expose the uterosacral ligaments (USL). The ischial spines and sacrospinous ligaments are identified bilaterally. An Allis clamp is placed on the distal uterosacral ligament and placed on traction to allow palpation of the uterosacral ligament. The sutures are placed as cephalad as possible on the USL to minimize ureteral injury. Two or three permanent or delayed absorbable sutures are placed through the proximal uterosacral ligaments and vaginal apex bilaterally. If an anterior colporrhaphy is required, it is then performed. The anterior vaginal wall incision and vaginal cuff are closed. Indigo carmine should be administered intravenously and cystoscopy performed to confirm patency of the ureteral orifices.

Complication rates for USLF, as described by a large meta-analysis by Margulies et al. (American Journal of Obstetrics & Gynecology 2010) are similar to SSLF:

- Ureteral obstruction – 1.8 percent

- Blood transfusion – 1.3 percent
- Pelvic organ injury – 0.4 percent

Ten studies reported on perioperative morbid events for 820 women who underwent a uterosacral ligament suspension in combination with other prolapse repair procedures. Ureteral obstruction was the most common complication and was reported in 15 cases (1.8%). Ureteral reimplantation was required in 5 cases (0.6%). Blood transfusion was reported in 11 cases (1.3%). Intraoperative complications also included a cystotomy during hysterectomy (0.1%) and 2 cases of bowel injury (0.2%). Unger et al. (2014) performed a retrospective study of 983 USLF patients with specific focus on perioperative and postoperative adverse events. 10 patients had bladder injury, 44 patients had ureteral kinking, 5 patients required return to the OR within the perioperative period (mostly for bowel obstruction), 11 patients had post op neurologic injury, 200 patients had post op urinary tract infections and 5 patients had unrecognized ureteral injuries. (Unger, C. et al., Incidence of adverse events after uterosacral colpopexy for uterovaginal and posthysterectomy vault prolapse, Amer. J. of Obstet. & Gyn. Vol. 212, Issue 5, May 2015, 603.e1–603.) Ureteral obstruction is the most common complication of USLF and is significantly higher than in SSLF. Cystoscopy should be done routinely at the completion of each case to prevent delayed recognition of ureteral injury.

The sacral nerves can be injured as they pass on the lateral border of the USL (Siddeque SA et al., Relationship of the uterosacral ligament to the sacral plexus and to the pudendal nerve, Int. Urogyn. J. Pelvic Floor Dysfunct. 2006). Sensory neuropathy and pain in the S2 to S3 dermatomes immediately postoperatively has been reported as well. (Flynn MK, et al., Sensory nerve injury after uterosacral ligament suspension Am. J. Obstet. Gynecol. 2006).

In terms of sexual function, Silva et al. reported that there was an abnormality in sexual

desire and overall sexual function, as assessed by the Female Sexual Function Index but that 94% of women who were sexually active before and after surgery reported "normal satisfaction" with their sexual lives. (Silva et al, Uterosacral ligament vault suspension: five-year outcomes, Obstet. Gynecol. 2006). Preoperative dyspareunia was relieved in all patients. However, 20.8% of the cohort experienced de novo dyspareunia. In contrast, Amundsen et al. reported that "no patient who was sexually active preoperatively reported sexual difficulty or dyspareunia." (Amundsen et al., Anatomical correction of vaginal vault prolapse by uterosacral ligament fixation in women who also require a pubovaginal sling, J. Urol. 2003).

Outcomes of transvaginal repairs

Although multiple studies have been reported in the literature, there are surprisingly few high quality studies such as randomized controlled trials on transvaginal native tissue prolapse procedures. Early cohort studies of sacrospinous ligament and ileococcygeus colpopexy show the operations to be effective for vaginal apex support, but vaginal prolapse recurs with time, most commonly the anterior wall. With a 73-month follow-up in 243 patients who had had sacrospinous ligament colpopexy and vaginal repairs, Paraiso et al. reported prolapse recurrence in the anterior, posterior, and apical segments to be 37.4%, 13.6%, and 8.2%, respectively. Prolapse-free survival rates at 1, 5, and 10 years were 88.3%, 79.7%, and 51.9%, respectively. From 1981 to 1993, Shull and Meeks et al. used the iliococcygeus colpopexy technique to treat 152 patients with post- hysterectomy vault prolapse or total uterine prolapse. Thirteen (8%) patients developed recurrent pelvic support defects at various sites 6 weeks to 5 years after the initial procedure; two had apical prolapse, eight had anterior vaginal prolapse, and three had posterior wall defects.

In 2000, Shull and colleagues reported on their experience with 298 patients after uterosacral ligament colpopexy. Twelve percent had evidence of an anterior wall defect in the form of cystocele or urethrocele and 4% of patients developed posterior wall defects. In all, 38 patients (13%) had development of one or more support defects. A more recent systematic review of uterosacral ligament colpopexy showed that, in the anterior, apical, and posterior vagina, the pooled rates for successful anatomic outcome were 81.2%, 98.3%, and 87.4%, respectively. Patients with more severe POP (stage III or IV) had significantly worse cure rates. However, these results have not been reproduced in trials where stricter criteria for success were used. (M. Barber, L. Brubaker, I. Nygaard, et al., Defining success after surgery for pelvic organ prolapse. Obstet. Gynecol. 114 (3) (2009), pp. 600–609.) Furthermore, anterior compartment recurrence rates after transvaginal native tissue repairs have been calculated as high as 40%. (Morgan DM et al., Heterogeneity in anatomic outcome of sacrospinous ligament fixation for prolapse. Obstet Gynecol. 2007;109(6):1424-1433.)

In 2014, Barber et al. published the Optimal trial in JAMA which was a randomized controlled trial comparing SSLF and USLS in 374 women with stage 2 to 4 prolapse with 2 years of follow up. The design used strict criteria for success of repair, including anatomic data such as POPQ physical examination and subjective degree of bothersome bulge symptoms. They found no difference between the two techniques at 2 years, but outcomes for both procedures were surprisingly poor (ULS, 59.2**%** [93/157], vs SSLF, 60.5% [92/152]). Overall, 18.0% of women (55/305) developed bothersome vaginal bulge symptoms, 17.5% (54/308) had anterior or posterior prolapse or both beyond the hymen, and 5.1% (16/316) underwent retreatment with either a pessary or surgery by 2 years.

Apical repair – Abdominal Approach

The abdominal sacral colpopexy (ASC) is a surgery to connect the vaginal vault/cervix to the anterior surface of the sacrum at the anterior longitudinal ligament. This procedure, first described by Savage et al. in 1957, restores the normal axis of the vagina and preserves vaginal length which is important in patients who desire continued sexual activity and in those with an already foreshortened vagina from previous surgery. The procedure has evolved in modern time to employ the use of synthetic suspension material which both relieves the tension that would be required to suture the apex to the sacrum and provides a source of strength in patients for whom the native tissue with prolapse is weak.

The procedure is done through a low midline or a Pfannenstiel incision. In patients who have a uterus, a supracervical or total hysterectomy is performed first. Then the vesicovaginal and rectovaginal spaces are developed. A monofilament, large pore polypropylene (Type 1) Y-shaped piece of mesh is attached to the vaginal apex/cervix and vaginal walls using interrupted full thickness permanent sutures such as Prolene or GORE-TEX. Then the sacral promontory is identified and the overlying peritoneum is incised while retracting the sigmoid to the left. The anterior longitudinal ligament is exposed and several interrupted permanent sutures are placed through the longitudinal ligament and periosteum of the sacrum. These sutures are then passed into the long arm of the Y-shaped graft and tied down. The peritoneum is then closed over the graft for retroperitonealization. The procedure can be performed in combination with a Burch colposuspension for incontinence, or with vaginal surgery such as anterior and posterior repair with sling.

The Maher Cochrane Review (2010) of the surgical management of POP identified 40

randomized controlled trials that compared vaginal sacrospinous ligament suspension to ASC. ASC resulted in a decreased rate of recurrent vaginal vault prolapse, decreased incidence of dyspareunia and lower stage of residual prolapse vs. vaginal repairs. Benson et al. performed a randomized study comparing bilateral sacrospinous fixation to ASC with a mean follow-up of 2.5 years. (Benson et al., Vaginal versus abdominal reconstructive surgery for the treatment of pelvic support defects: a prospective randomized study with long-term outcome evaluation. Am. J. Obstet. Gynecol 1996**).** The ASC group was twice as likely as the sacrospinous group to have an optimal outcome (58% vs 29%) and 50% less likely to require reoperation (16% vs 33%). The vaginal vault recurrence rate was 2.6% in the ASC group vs 12% in the sacrospinous group.

In the Colpopexy and Urinary Reduction Efforts (CARE) trial, stress-continent women undergoing sacrocolpopexy were randomized to receive or not receive a Burch colposuspension (Brubaker et al. OBGYN 2008). They also looked at 2 year functional and anatomic outcomes of apical support and found 95% of women had point C on a POPQ no less than 2 cm of TVL. A recent long term extension of the CARE trial (Nygaard et al., JAMA 2013) showed that ASC may not be as durable as previously theorized. These authors found that by 7 years, surgical failure defined as either self-reported bulge or anatomic POP failure requiring retreatment or Pelvic Organ Prolapse Quantification evaluation demonstrating descent of the vaginal apex below the upper third of the vagina, or anterior or posterior vaginal wall prolapse beyond the hymen was found in nearly one third of patients by 5 years.

Complications associated with ASC can be divided into early and late. Most early complications including intraoperative complications consist of injury to pelvic structures, infection, thrombotic events, hemorrhage and ileus. Pelvic structures subject to injury during ASC include bowel, bladder and ureters, and if injury is identified intraoperatively, management

usually consists of a primary repair. Cystoscopy may be considered at the end of the case to evaluate for bladder injury and verify efflux of urine from both ureteral orifices. Life-threatening bleeding from the presacral space is rare but one of the most feared complications of sacral colpopexy. When there is bleeding from presacral vessels, hemostasis can be difficult to achieve because of the complex interlacing of the venous network both beneath and on the surface of the sacral periosteum. When these veins have been injured, they can retract beneath the bony surface of the anterior sacrum. Communications with adjacent pelvic veins, especially the left common iliac vein, can be particularly troublesome. If this complication should occur during a laparoscopic or robotic sacral colpopexy, it would lead to a rapid open conversion. Need for open conversion in the literature is approximately 5%. (Rozet F. et al., Laparoscopic sacral colpopexy approach for genito-urinary prolapse: experience with 363 cases, Eur. Urol. 2005).

In a systematic review of 65 studies of open ASC, Nygaard et al. (2004) noted a mean incidence of bladder injury of 3.1% and a mean incidence of ureteral injury of 1%. Bowel injury was reported with mean of 1.6% of open repairs. Wound infections, including pelvic abscess or vaginal cuff infection, occurred infrequently but urinary tract infections were more common with rates up to 26% (median 11%). Other early complication rates reported were bleeding or transfusion 4.6%, ileus 3.6% and deep vein thrombosis 3.3%. Complications that may occur after the immediate postoperative period include small bowel obstruction (1.1%), mesh erosion (3.4%) and incisional hernia (5%). Other complications that can occur any time are de novo SUI, urge incontinence and other voiding dysfunction not present preoperatively.

One particularly challenging complication of abdominal sacral colpopexy is mesh exposure. In many cases, such exposures are located at the apex of the vagina which can be

difficult to excise from a transvaginal approach. Some authors have proposed that factors which may increase the incidence are smoking history, full (as opposed to supracervical) hysterectomy and type of graft material utilized. (Wu JM et al., Mesh erosion in abdominal sacral colpopexy with and without concomitant hysterectomy, Am. J. Obstet. Gynecol. 2006). In the literature, exposure rates have ranged from 3 to 8%. (Begley JS, et al., Incidence and management of abdominal sacrocolpopexy mesh erosions. Am. J. Obstet. Gynecol. 2005; Cundiff GW, et al. Risk Factors for Mesh/Suture Erosion Following Sacrocolpopexy, Am. J. Obstet. Gynecol. 2008). In the Nygaard JAMA study (2013) which was a 7-year follow up on the original CARE trial, there was a surprising estimated rate of mesh and suture exposure of 10.3%.

In addition to the potential complications already described for open approaches, laparoscopic and robotic assisted procedures are associated with their own set of unique potential complications. The need for 'steep' Trendelenburg, a bed positioning in which the table is tilted with the head down and the legs high in the air in order to move the intestines out of the pelvis and into the upper abdominal cavity, can lead to difficulty with ventilation of the morbidly obese patient or those with underlying pulmonary disease. Complications with pneumoperitoneum have been reported. (Mahran MA et al., Laparoscopic management of genital prolapse Arch. Gynecol. Obstet. 2011). Furthermore, there is a steep learning curve with minimally invasive techniques, which may result in increased operative time compared to the open approach. Increased operative time and use of disposable instruments increase the cost of the procedure as well. (Paraiso M. et al., Laparoscopic and abdominal sacral colpopexies: a comparative cohort study Am. J. Obstet. Gynecol. 2005).

Introduction of Transvaginal Meshes to Repair POP

Transvaginal mesh has offered several potential advantages over existing types of repairs. Transvaginal mesh-augmented repairs for POP evolved with the goal of reducing the invasiveness and morbidity of the abdominal approach, while also providing improved anatomic outcomes and durability over native tissue repairs. Mesh reinforcement is not new to the field. The first mesh repairs were performed in the 1950's with tantalum metal but were associated with significant erosive complications. (Moore, J et al., Am. J. Obstet. Gynecol. 1955;69:1127–35). Friedman and Melzer used collagen mesh in the 1970s to augment prolapse repair. (Am. J. Obstet. Gynecol. 1970 Feb). The first trial to compare mesh vs. non-mesh repairs in the management of posterior wall vaginal prolapse was published by Sand et al. in 2001. In this study, absorbable Vicryl mesh was used for the augmented repair arm. The authors found virtually no difference in prolapse recurrence rates between the two groups.

Nowadays, the most common adjuvant mesh graft for POP is synthetic mesh made of non-absorbable polypropylene. It is described as type 1 in the Amid classification system based on pore size (microns) and filamentous structure (monofilament vs multifilament). Pore sizes larger than 75μ are considered ''macroporous.'' The relatively larger pores of macroporous mesh allow passage of macrophages, fibroblasts and collagen fibrils to permit immune permeability and ingrowth of tissue. Smaller pore sizes and the structure of multifilament meshes may be of such a size as to permit bacteria within its interstices but not essential components of the immune system and/or connective tissue ingrowth. (Amid, Hernia, 1997). There have been numerous studies on this type of graft in the treatment of apical prolapse such as ASC. The safety of this approach has been well established in numerous studies reported over the last several decades. The use of transvaginal mesh was initially adopted on a large scale after the introduction of

synthetic slings for the treatment of urinary incontinence. (Ulmsten U., An Ambulatory Surgical Procedure Under Local Anesthesia for Treatment of Stress Urinary Incontience, Int. Urogyn. J. (1996) 7:81-86). The safety of synthetic mesh slings has been well established over the last 17 years. The use of synthetic mesh slings for urinary incontinence has shown significant efficacy, durability, and safety, and led the way for innovation towards transvaginal mesh prolapse repairs. This was an intuitive step on the progression of improved transvaginal repairs, especially since biologic and absorbable synthetic mesh trials in the past had failed to demonstrate superiority to traditional repairs.

In 2001, the FDA approved the first transvaginal mesh kit to repair prolapse, the posterior intravaginal sling-plasty (US Surgical, Tyco Healthcare Group, Norwalk, Connecticut) (Farnsworth BN: Posterior intravaginal slingplasty (infracoccygeal sacropexy) for severe posthysterectomy vaginal vault prolapse – a preliminary report on efficacy and safety. Int. Urogyn. J. Pelvic Floor Dysfunct. 2002). For this procedure, a multifilament polypropylene tape (type 2 mesh) was tunneled through the ischiorectal fossa to create support at the level of the cardinal ligament for vaginal vault prolapse. Due to complications likely related to the multifilamentous nature of the mesh, this device was discontinued.

In 2002, Gynemesh PS was cleared for the market with an indication covering both abdominal and transvaginal repair of prolapse. During my fellowship training and even into the first few years of my independent practice, this was the primary approach I used to correct symptomatic pelvic organ prolapse. In a technique that was described by Shah DK et al. (Short-term outcome analysis of total pelvic reconstruction with mesh: The vaginal approach. J. Urol. 2004; 171:261-3.), a piece of Gynemesh was cut by the surgeon and used to augment the anterior

vaginal wall by placing sutures through the mesh and then performing an anterior approach to the sacrospinous ligament bilaterally. Additional anchoring sutures would tack the mesh to the arcus tendineous facia pelvis (ATFP) on either side to secure the mesh distally. In our procedures, we would use the CAPIO suture capturing needle device to drive the anchoring sutures through the ligaments. A concomitant transvaginal hysterectomy, mid urethral sling and/or posterior repair was performed concomitantly when necessary. It was not until I was introduced to transvaginal mesh kits that I began to change my surgical technique.

Gynecare Prolift Pelvic Floor Repair System

In June of 2000, the collaboration of the 'TVM group' of surgeons began in Nice, France. The group, which was comprised of nine experienced pelvic floor surgeons, set out to devise a procedure using a transvaginal mesh which would be more uniform in approach, safe, durable and well tolerated by the body. They chose the implant to be Gynecare Gynemesh PS® (Ethicon, Somerville, New Jersey, USA), a low-weight (42.7 g/m^2), thin (0.42 mm) and high-porosity (64%) synthetic, Amid type 1 polypropylene prosthesis. The surgical procedure was refined over a 5-year period through more than 600 surgical interventions by the nine French surgeons. The group assessed implant shapes and sizes, material composition, incisions, dissection techniques and implant fixation points. (Berrocal et al. (2004); Cosson, M. ICS Abstract (2005)).

The product that evolved from this process was Gynecare Prolift Pelvic Floor Repair System. It includes a non-absorbable implant made of Gynemesh PS which comes in three pre-cut versions. The anterior part was intended for insertion between the bladder and the vagina and secured bilaterally by two sets of arms through each obturator foramen, correcting anterior

wall prolapse. The posterior part, placed between the rectum and the vagina, and secured bilaterally by one arm passing through each ischiorectal fossa and sacrospinous ligament corrected posterior wall prolapse. The intermediate section, corresponding to the vaginal apex was used if necessary in post hysterectomy patients. The instruments were designed to facilitate proper implant placement and ensure a tension free placement of the product. Cannula-equipped guides were used to optimize the passage through the tissues, preventing muscle trauma and disruption of the arcus tendinous fascia pelvis (ATFP) and to allow the placement of the retrieval device. Retrieval devices were provided to easily catch and smoothly pass each prosthesis strap through the pelvis. In most cases a hysterectomy could be avoided. (Fatton et al. 2007).

The procedure could be performed on women with all stages of prolapse but was best suited for those with more advanced stages of prolapse. (Prolift Surgeon's Resource Monograph, pg. 3). After administration of spinal or general anesthesia, patients were carefully positioned in the lithotomy position with thighs flexed at approximately 90°. After cleaning the entire surgical area with antiseptic, a urine culture is performed and an in-dwelling catheter is placed. Intravenous perioperative antibiotic prophylaxis is recommended as per surgeon preference. The vaginal wall is infiltrated with saline mixed with a vasoconstrictive solution to ease dissection and reduce bleeding. Beginning with the anterior dissection, a vertical incision is made starting 2 cm away from the cervix and ending approximately 2 cm from the bladder neck. It is important for the incision be of the proper depth, in the true vesicovaginal space, and that the bladder is dissected laterally while keeping the pubocervical fascia on the vaginal wall. After opening the paravesical fossa, palpation via a finger can identify the arcus terndineuous fascia pelvis (ATFP), which extends from the posterior aspect of the pubic arch to the ischial spine. Next, four skin incisions are made on the genitocrural crease: two incisions on the anteromedial

edge of the obturator foramen at the level of the urethra and the two other incisions 2 cm below and 1 cm lateral to the first ones. Bilateral passage of the two upper cannula-equipped guides at 1–2 cm of the prepubic part of the ATFP and bilateral passage of the two lower cannula-equipped guides at 1–2 cm of the distal part of the ATFP (1 cm from the ischial spine) allows to catch each prosthetic arm and pass them through the obturator foramen (Fig. 3b and c). Afterwards, the mesh is positioned tension-free under the bladder. The center points of the mesh can be fixed to the bladder neck and cervix with absorbable or non-absorbable suture prior to tensioning. The anterior wall is closed with running absorbable suture.

For the posterior part, a short vertical incision is performed similarly to the anterior incision. The entire thickness of the posterior vaginal wall is dissected while keeping the rectovaginal fascia on the vaginal mucosa. The pararectal spaces are opened and dissection is performed between the rectum and the levator ani muscle plane until the sacrospinous ligament can be palpated. A skin incision is made 3 cm lateral and 3 cm down from the anus. Another cannula-equipped guide is inserted into the incision, passed through the buttock and the ischiorectal fossa until it reaches the middle part of the sacrospinous ligament, 1 cm medial to the ishial spine. The cannula is left in place. The procedure is repeated on the opposite side. The posterior arm is retrieved using the retrieval device and once it passed through the ischiorectal fossa, the posterior mesh is positioned over the rectum medially and the levator ani muscles laterally. The mesh is also fixed to the posterior part of the cervix. The posterior wall is closed with running absorbable suture. Tension on the anterior and posterior meshes is adjusted before removing the cannulas. This is performed with closed vaginal wall and manual compression of the deepest portion of the implant to keep the device from overtightening. No excision of vagina wall is necessary. At the end, a rectal examination is performed to check for

rectal laceration or any stricture of the rectal lumen. Cystoscopy is also performed to ensure bladder and ureteral integrity.

The procedure can be performed in whole, as with a total kit, or in part with anterior or posterior only implants depending on the surgeon's assessment of the pelvic anatomy. If a simultaneous hysterectomy is necessary, a separate incision is recommended for the anterior Prolift and hysterectomy with the hysterectomy site closed horizontally and the Prolift site closed vertically. For optimal healing, they should not intersect (T incision). After the procedure, an anti-incontinence procedure (ie. midurethral sling) can be performed as well as perineorrhaphy. A foley catheter and lubricated vaginal packing is put into the vagina for 24 to 48 hours. The Prolift Surgical Technique Guide (2005) provides a detailed description for the surgeon on proper mesh placement in multiple scenarios.

My Experience with Prolift

During my residency and fellowship training I was exposed to numerous transvaginal and transabdominal procedures for the treatment of POP. I began to use synthetic polypropylene mesh to augment the anterior and apical vaginal wall during my fellowship training. In this procedure we would cut our own mesh, usually Gynemesh PS, and anchor the implant to sacrospinous ligaments through an anterior approach (incision in the anterior vaginal wall) and into arcus (ATFP) on both sides. The results were excellent anterior and apical suspension but many of the patients experienced pain during the recovery periods because we were not using a tension free approach. This procedure has been described elsewhere in the literature. (Nicita, 1998; Badlani 2007). The neuropathic pain which might accompany "sewn-in" mesh placed

under tension has also been well described. (Huebner and Fenner, The use of graft materials in vaginal pelvic floor surgery, 2006).

When I started to use Prolift regularly in 2007 I was already familiar with the pelvic anatomy and the necessary dissection, as well as the obturator approach which I was employing in using the TVT-O sling to treat SUI. Nonetheless I went to a training course to learn the nuances of the technique and realized that there were important steps such as deeper placement of the mesh which would prevent some of the mesh complications I had seen with my other repairs. I was immediately impressed by the quality of the repair without increased morbidity to the patient. In order to reproduce the same procedure I had learned in my fellowship, I was initially not following the IFU for Prolift. Instead, I was cutting and pasting the total kit and introducing the posterior arms through an anterior approach to the SSLF. My main reason for doing this was I was uncomfortable placing mesh over the back wall of the vagina. As a result, I had excellent anterior and apical support but a fair amount of postoperative uterine prolapse, high posterior enterocele and rectocele recurrences. However, in later years I began to follow the IFU more closely. The result was excellent. I had very few recurrences and my exposure rate was under 3%. I found that performing a total procedure prevented recurrence in this area with few adverse events.

I was very disappointed when Prolift and Prolift +M were discontinued in 2012. By that time, I had become so experienced with the procedure and my complication rate was negligible, I felt like a carpenter without a hammer and nails. It occurred to me that the Prolift products, when placed safely by experienced hands, were revolutionary treatments for pelvic organ prolapse. The complications that I saw such as occasional mesh exposures were usually

asymptomatic and treated by local excision if necessary. I never felt that going back to the OR for removal of a mesh exposure was as drastic as return to the OR for a recurrence. With over 500 Prolift procedures, I never saw mesh erosion into the rectum or bladder, never had a ureteral injury or major nerve injury. In my hands, I could imagine no safer or effective procedure to eradicate prolapse disease.

Clinical Literature

There have been several short and mid-term studies series on the TVM procedure. Miller et al. (2011), using the strict criteria of no greater than stage 1 prolapse on POPQ, studied sixty-six women for a follow-up of 5 years. Overall anatomic success rates were 88%, 69% and 67% at 1, 3, and 5 years, respectively. Anatomic success rates in treated compartments were 89%, 76% and 77% at 1, 3, and 5 years, respectively. Long et al. (2012) studied 124 patients and defined recurrence as the most distal portion of POP stage II or greater. At three years, the overall success rate was 93.5% (116/124). Various urinary symptoms improved significantly following TVM ($P < 0.01$). In addition, residual urine, functional urethral length, and the rate of detrusor overactivity, improved significantly after surgery ($P < 0.05$). The vaginal erosion rate was 14/124; 11.3%, and the rates of other surgical complications were low. Caquant et al. (2008) described initial data on the original Prolift procedure in 684 patients with grade 3 and higher prolapse. Relapse of prolapse was 6.9%. Jacquetin (2012) presented 5 year follow up data on 82 patients after Prolift for the treatment of stage 2 and higher prolapse. Success was defined as no surgical prolapse reintervention and leading edge <−1 (International Continence Society [ICS] criteria) or above the level of the hymen, was 79 % and 87 % respectively. A composite criterion of success was utilized, defined as: leading edge above the hymen (<0) and no bulge symptoms and no reintervention for prolapse was met by 90%, 88 % and 84 % at the 1-, 3-, and

5-year endpoints respectively. Quality of life improvement was sustained over the 5 years. Benzoubid (2012) studied 75 patients with a mean follow up of 53.7 months (range 36–72 months). Cure was defined as an anatomical success at last follow up, being a Pelvic Organ Prolapse Quantification stage 1 without further surgical intervention in any compartment. 64 (85.3%) patients were cured, with no prolapse recurrence. Mesh exposure occurred in four (5.3%) patients. The Pelvic Floor Distress Inventory-20 symptom score was low at last follow up (median 8, range 3–18), in accordance with objective cure data. Kozal et al (2014) presented their 7 year experience with 112 patients, 66% of which had stage 3 or greater prolapse and were treated with Prolift. The median follow up was 49. 5 months. They reported a failure rate of 8% (n = 9) occurring after a median follow- up of 9.5 months (range: 1-45).

There have been several excellent reviews of the RCT data comparing mesh to native tissue repairs. For anterior POP repair, TVM use has been shown to improve durability and anatomic outcomes in several studies, particularly when stricter anatomic criteria are used. In a meta-analysis, Jia et al. found that any form of mesh or graft used for anterior compartment repair resulted in reduction of objective POP recurrence rates compared to no mesh at short-term follow-up. Furthermore, they reported a statistically significant reduction in objective prolapse recurrence rates with non-absorbable synthetic mesh compared to absorbable mesh and biological graft. (Jia X et al., Efficacy and safety of using mesh or grafts in surgery for anterior and/or posterior vaginal wall prolapse: Systematic review and meta-analysis. BJOG 2008).

Menefee et al. (Obstet. Gynecol. 2011) compared anterior colporrhaphy with paravaginal repair alone or with polypropylene mesh or porcine dermis. In this RCT of 99 women with 2-year follow-up a significantly lower anatomic failure rate was noted in the mesh (18%) than in the porcine (46%, p=0.015) and colporrhaphy (58%, p= 0.002) groups but no difference was

found in composite failure measures including anatomic and quality of life outcomes among the 3 groups (13% colporrhaphy, 12% porcine and 4% mesh). Similarly, Withagen et al. (2011) reported a twelve month post-surgery anatomic failure in the treated compartment of 38 out of 84 patients (45.2%) in the conventional anterior colporrhaphy group and in eight of 83 patients (9.6%) in the mesh group. Halsaka (2012) performed a randomized trial of patients with vaginal vault prolapse; 83 underwent SSLF and 85 underwent Prolift total mesh repair. Prolapse recurrence after 12 months was much higher the SSLF group (39.4%) compared with the Prolift group (16.9%) (P .003). Similarly, Svabik et al (2014) confirmed a higher failure rate in posthysterectomy prolapse patients with SSLF versus Prolift treatment.

Altman et al. (NEJM 2011) compared 186 patients treated with Prolift to 182 treated with anterior colporrhaphy. The primary outcome was a composite of the objective anatomical designation of stage 0 (no prolapse) or 1 (position of the anterior vaginal wall more than 1 cm above the hymen), according to the Pelvic Organ Prolapse Quantification system, and the subjective absence of symptoms of vaginal bulging 12 months after the surgery. At 1 year, the primary outcome was significantly more common in the women treated with transvaginal mesh repair (60.8%) than in those who underwent colporrhaphy (34.5%). De Silveira et al. (2015) reported results from a multicenter trial including 184 women with high grade genital prolapse randomized to native tissue and synthetic mesh repair with Prolift. The results showed superior anatomic efficacy in the mesh group only in the anterior compartment; quality of life measures were superior in the mesh group. Complications specifically regarding mesh exposure were more frequent in the mesh group.

Although the literature on the use of TVM in the posterior compartment is less developed, posterior mesh can play a very important role in preventing prolapse recurrence. In

the study by Sokol et al., the recurrence rate in the posterior mesh group was 21.9% vs 18.2% in the non-mesh group with no statistical significance. Withagen et al. reported an RCT with a larger number of patients undergoing posterior repair (posterior TVM in 56 women). The 4.1% posterior recurrence rate after posterior TVM was significantly lower than the 24.5% recurrence rate after traditional repair. Secondary analysis of this study revealed that mesh repair in the posterior compartment led to a significantly higher rate of de novo prolapse elsewhere (53%) compared to traditional colporrhaphy (17%). Carey et al. (2009) randomized 128 patients to anterior and posterior repair with and without mesh. Despite the the 12-month success rate in the mesh group of 81% using strict criteria vs the 65.6% success rate in the non-mesh group, these numbers did not reach statistical significance.

The Maher Cochrane review (2016) is a systematic review of 37 randomized controlled trials (RCTs), 4023 women, comparing different types of vaginal repair (mesh, biological graft, or native tissue). When comparing TVM to native tissue repair, this high quality review showed:

- Native tissue vs. mesh repair awareness of prolapse at one to three years was less likely after mesh repair
- Rates of repeat surgery for prolapse were lower in the mesh group.
- More women in the mesh group required repeat surgery for the combined outcome of prolapse, stress incontinence, or mesh exposure (RR 2.40, 95% CI 1.51 to 3.81, 7 RCTs, n = 867, I^2 = 0%, moderate-quality evidence).
- Recurrent prolapse on examination was less likely after mesh repair
- Permanent mesh was associated with higher rates of de novo stress incontinence (RR 1.39, 95% CI 1.06 to 1.82, 12 RCTs, 1512 women, I^2 = 0%, low-quality evidence) and

bladder injury (RR 3.92, 95% CI 1.62 to 9.50, 11 RCTs, n = 1514, I^2 = 0%, moderate-quality evidence). There was no evidence of a difference between the groups in rates of de novo dyspareunia.

Regarding the findings of increased rate of bladder injury and stress incontinence with the use of mesh, the Prolift IFU warns of these risks under the Precautions ("Prolapse repair may unmask pre-existing incontinence conditions") and the Adverse Reactions (**"**Punctures or lacerations of vessels, nerves, bladder, urethra or bowel may occur during Gynecare Prolift guide passage and may require surgical repair.")

In 2016, the SGS systematic review group performed a systematic review of 66 comparative studies including 38 randomized trials on native tissue repair versus graft augmentation. In the publication of this review, Schimpf et al. reported:

1. There is no difference in anatomic or quality-of-life outcomes when mesh is used in the posterior compartment compared with native tissue.
2. In the anterior vaginal compartment, synthetic nonabsorbable mesh consistently showed improved anatomic and bulge symptom outcomes compared with native tissue repairs.
3. Subjective outcomes, including urinary incontinence and dyspareunia, generally did not differ between mesh and non-mesh groups.
4. Mesh erosion occurred in up to 36% of patients, but reoperation rates were low (3-8%).

The authors concluded that "there is no universal answer to what prolapse surgery to perform in a specific situation because no prolapse or patient is identical. The data reported here

provide part of the picture, which also include surgeon experience, patient surgical history, desired sexual functioning, and related symptoms such as incontinence or bowel issues. We encourage surgeons to consider these factors when planning surgery as well as incorporating them into a thorough consent process."

I completely agree with this statement as it underscores the fact that the ultimate decision about what procedure to perform should be between the surgeon and the patient. There is no reason why a mesh augmented repair should not be offered to a patient if the surgeon is comfortable and confident with the repair and the patient understands the particular risks and outcomes of that procedure in that surgeon's experience.

Potential Complications

As previously discussed, any procedure for POP poses a risk of complications. There are two general theories that explain the occurrence of mesh complications. The first is that synthetic mesh implanted in the vagina is simply prone to causing pain, exposure, and perforation. There is little data to support this claim. The other and more likely scenario is that problems with appropriate surgical technique account for many mesh complications. With careful attention to patient selection, patient's anatomy, proper dissection into appropriate spaces and understanding the medium involved and its properties along with proper implantation techniques, many mesh complications can be avoided. Regardless, there are intra- and postoperative complications related to the use of mesh.

Exposure:

A complication which is unique to TVM is mesh exposure. The International

Urogynecological Association and International Continence Society jointly defined a terminology and classification system for mesh complications by category (c), time (t) and site (s). (Haylen BT, et al., An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint terminology and classification of the complications related directly to the insertion of prosthesis (meshes, implants, tapes) and grafts in female pelvic floor surgerys. Neurourol. Urodyn. 2011.)

Based on RCT data, rates of vaginal exposure after TVM POP repair with polypropylene mesh range from 3% to 35% and average of 12% with follow-up of 10 to 24 months. (Deffieux X, Letouzey V, Savary D et al: Prevention of complications related to the use of prosthetic meshes in prolapse surgery: guidelines for clinical practice. Eur. J. Obstet. Gynecol. Reprod. Biol. 2012; 165: 170.) The trial with the highest rate of exposure was in patients undergoing concomitant hysterectomy. (Lopes, ED (2010)). Some studies have indicated increased risk of exposure with TVM placement at the time of hysterectomy while others show no difference. European guidelines advise against concomitant hysterectomy at the time of TVM POP repair.

Although mesh exposure is not a complication seen in traditional surgeries that do not employ a mesh, other types of graft materials used in POP surgery do present a risk of exposure. Allografts and biologic materials have been shown to have equivalent rates of exposure to mesh. In most cases, allograft extrusions are managed nonsurgically. Abed (2010) performed a meta-analysis of 110 studies and revealed similar exposure rates after use of synthetic (10.3%, 91 studies, 10,440 cases) and biological (10.1%, 19 studies, 1345 cases) grafts. The reported timing of diagnosis of graft exposure ranged from 6 weeks to 12 months.

Risk factors related to mesh exposure have not been completely elucidated. Factors that

have been reported to predispose to mesh exposure include depth of vaginal dissection, quality and estrogenization of tissue, impaired healing (ie smoking, steroids), infection, hematoma formation and quality of vaginal closure. The most commonly seen presentation of mesh exposure includes mesh visible at a previous suture line, without any evidence of inflammation/granulation and well incorporated into the adjacent intact vaginal epithelium. This pattern of mesh exposure suggests a common mechanism for development of mesh exposure: separation of a suture line due to suture failure, or a process behind the suture line such as hematoma. Many surgeons believe that this is the most common cause for the development of type 1 mesh exposure. (Wu P.Y. et al., Int'l. Urogynecol. J. 2016 Oct). Less common presentations include exposure along a vaginal sulcus, along unincised vaginal mucosa, or visible fibers through intact, thin epithelium. Here perforation of the sulcus by the implantation needles (or trocar), 'button-holing' of the epithelium during dissection or progressive epithelial thinning due to urogenital atrophy are likely the primary causes. Several surgical methods or variations have been suggested to minimize the risk of vaginal exposure such as thicker vaginal flaps, smaller incisions and deep hydro-dissection.

Mesh exposure is often asymptomatic and not dangerous. Management of mesh exposure may include watchful waiting, administration of topical estrogen preparations, mesh trimming and mesh excision. However, the exact indications for these interventions as well as the optimal timing and performance of such maneuvers are not well defined in the medical literature. Considerations before intervention include the degree of symptomatic bother; sexual activity; size, location and duration of mesh exposure; and patient wishes. It is widely practiced and believed that, in general, small asymptomatic exposures can usually be successfully managed conservatively with pelvic rest and localized estrogen cream, or if necessary, in-office

excision. Larger and symptomatic exposures may require surgical excision (either partial or complete) to remove the exposed implant.

Erosion:

Erosion (or perforation) into the urethra, bladder or bowel is fortunately an uncommon event. It has been suggested that these complications may result from injury to neighboring viscera at the time of TVM placement. (Davila JW and Jijon A: Managing vaginal mesh exposure/erosions. Curr. Opin. Obstet. Gynecol. 2012). Treatment of visceral erosion diagnosed postoperatively would always requires endoscopic or open surgical removal. Although they rare events, all versions of the Proflift IFU have warned surgeons of the potential risk of extrusion or erosion.

Contraction

A complication of polypropylene mesh that is reported mostly in the hernia literature but mentioned in the 2011 FDA warning is mesh contraction, a shrinkage or reduction in the size of the tissue surrounding the mesh implant. Amid et al. reported that there is contraction of 20% to 30% during the period of incorporation and scar formation. (Amid PK, et al., A simple stapling technique for the prosthetic repair of massive incisional hernias (1972), In: Arregui ME, Nagan RF (eds) Inguinal hernia advances or controversies? Radcliffe Medical Press, Oxford, pp 511–514.) Because there is little to no data on vaginal mesh contraction, specifically Gynemesh PS or M, its clinical significance is uncertain. Some papers have hypothesized that fibrosis and scar contracture could result in mesh shrinkage over time which could explain complications such as pain, dyspareunia and erosion. Dietz et al found no evidence of mesh contracture in 40 patients who underwent anterior TVM repair using translabial 4-dimensional ultrasound.

Dyspareunia:

Dyspareunia is another complication that has been reported in association with TVM, although by no means is it exclusive to the use of mesh. In the Abed (2010) systematic review of the literature on 70 TVM studies the rate of dyspareunia was 9.1% (95% CI 8.2–10.0, range 0%–6.7%, synthetic 8.9%, biological 9.6%). The average rate of de novo dyspareunia after polypropylene TVM was 14% among 11 randomized or prospective studies.

Author	Year	*N*	De novo dyspareunia	Follow up (mos)
Withagen	2011	66	3/37 (8%)	12
Long	2011	48	12/48 (25%)	6
Sergent	2011	57	4/57 (7%)	57
Jacquetin	2010	39	6/39 (15%)	3
Moore	2010	65	6/65 (9%)	24
Cervigni	2008	218	21/28 (9.6%)	38
Lowman	2008	57	10/57 (17%)	12
Nguyen	2008	23	2/23 (9%)	12
Sentilhes	2008	37	6/37 (16%)	6
Sivaslioglu	2008	45	2/45 (4.5%)	12
De Tayrac	2007	78	10/78 (12.8%)	12
Total			61/438 (13.9%)	

In the Maher Cochrane Review published in 2016, there was little or no difference between the groups in rates of dyspareunia: vaginal surgery with mesh 5% (13/257) versus

vaginal surgery without mesh 4% (10/243) (RR 1.21, 95% CI 0.55 to 2.66; 5 RCTs, n = 501; I2 = 0%, moderate quality evidence Analysis 2.10). This data suggests that if dyspareunia occurs in 3% of women after vaginal surgery without mesh, then between 2% and 9% will have dyspareunia after vaginal surgery with mesh. For instance, in a randomized multicenter trial with 386 patients, comparing the placement of a mesh (PROLIFT™) with an anterior colporraphy, Altman et al. showed that the small improvements in the PISQ-12 were comparable between the two groups. In a randomized trial comparing the vaginal route with a mesh (polypropylene) and without a mesh, Nieminen et al. found no difference in the prevalence of sexual deterioration between the groups. Dietz and Maher also found no difference in sexual function between anterior repairs with and without mesh. (Dietz V., Maher C., Pelvic organ prolapse and sexual function, Intl. Urogyn. J. (2013) 24:1853-1857).

These findings are consistent with the study by Lowman (2008) which found no increased risk of de novo dyspareunia with Prolift (16.7%) as compared with other types of prolapse procedures that do not incorporate vaginal mesh (range 14.5 – 36.1%). Although 17% of patients developed de novo dyspareunia, 85% of patients were satisfied with their results and would have the surgery done again (75% of those with dyspareunia, 83% with de novo dyspareunia). The authors noted that the "patient's willingness to have this surgery again supports the fact that the presence or absence of dyspareunia, although significant, does not determine a woman's overall sexual health."

Furthermore, the ability of TVM to spare the uterus is one great advantage of the procedure when it comes to post-operative dyspareunia. Abdelmonem (2010) noted that

postoperative dyspareunia is more common after vaginal hysterectomy compared to abdominal hysterectomy. This may be attributed to postoperative shortening of the vagina secondary to mandatory trimming of the vaginal walls especially if VH is done for uterovaginal prolapse. In his study, dyspareunia in the VH group was 20%.

Finally, although many women observe that their sexuality does not change or is improved by prolapse surgery, patients must be informed of the risk of a dyspareunia, whatever route is used. With the vaginal route, this risk of deterioration appears to be comparable with or without the introduction of prosthetic material.

Pelvic pain:

The prevalence of pain associated with synthetic TVM varies between 4% and 11%, depending on the definition used. In most cases, postoperative pain resolves spontaneously and can be managed conservatively. Again, pelvic or abdominal pain is not unique to TVM procedures and has been reported with a variety of other POP procedures as well. (Chung CP et al., Recognition and management of nerve entrapment pain after uterosacral ligament suspension. Obstet. Gynecol. 2012). Pain resulting from a TVM POP procedure may be due to a variety of causes including excessive tension, improper anatomic placement, exposure, erosion, nerve entrapment or other neurological causes or other factors. There is concern that retraction or contraction of implanted material may lead to changes in vaginal caliber or length. Gauruder–Burmester et al. reported mesh shrinkage of 46% to 54% due to contracture but it was not associated with postoperative vaginal length measurement changes or sexual dysfunction. Dietz et al. found no evidence of mesh contracture in 40 patients who under- went anterior TVM repair using translabial 4-dimensional ultrasound. (Dietz HP, Erdmann M and Shek KL: Mesh

contraction: myth or reality? Am. J. Obstet. Gynecol. 2011; 204: 173).

Minimizing the risk of complications

All complications related to transvaginal mesh placement for prolapse can be reduced by good patient selection and proper training on surgical technique. Surgical technique is taught in residency and fellowship programs where surgeons learn proper tissue handling and how to work with various implant materials to minimize complications and maximize successful reversal of compartment defects.

There is evidence that complications are higher among providers with less surgical experience. In a study of 198 patients treated with surgical correction using mesh, the experienced surgeon had fewer exposures than the less experienced surgeons (2.9 versus 15.6 percent). (Achtari C. et al., Risk factors for mesh erosion after transvaginal surgery using polypropylene (Atrium) or composite polypropylene/polyglactin 910 (Vypro II) mesh. Int'l. Urogynecol J Pelvic Floor Dysfunct. 2005;16(5):389).

A key component of proper surgical technique of implanting Prolift is the use of a full-thickness dissection. That is accomplished via hydrodissection with development of a deeper surgical plane that leaves the pubocervical connective tissue attached to the epithelium. The rationale is to maintain vascular supply to the epithelium and improve healing, with the goal of diminishing graft exposure. In contrast, the traditional plication of the vaginal epithelium is separated from the underlying pubocervical connective tissue, which is subsequently plicated in the midline with a delayed absorbable suture (Prolift IFU). The need for full thickness dissection is well addressed in Prolift professional education materials. (See for example, 2007/2008 Professional Education slide deck, Prolift Surgeon's Resource Monograph). When I attended

my first Ethicon-sponsored training program on Prolift, precepted by Dr. Vince Lucente in Allentown PA, I was an avid TVM user using Gynemesh PS. Dr. Lucente showed me how to adequately hydrodissect in order to achieve the optimal tissue plane, a step that I had been omitting in my own repairs. The use of this technique reduced the frequency of exposures that I saw in my TVM repairs.

The surgeon must ensure that the mesh lies flat in the pelvis and there is no bunching or folding of the graft. Also critical is the tension free placement of the mesh. Excessive tension in the arms could lead to vaginal bands. Following correct placement of transvaginal mesh, there should still be persistent laxity of the vaginal wall to allow for mesh contraction during the postoperative period. Prior to completion of the procedure, the vagina and rectum should be checked, and the lateral arms of all grafts used should be checked to ensure they are not "tight" or under tension. If they are, they should be loosened prior to the patient leaving the operating room. The Prolift IFU warns that "users should be familiar with surgical procedures and techniques inyolving pelvic floor repair and synthetic meshes before employing the GYNECARE PROLIFT system" and "to avoid placing excessive tension on the *mesh* implant during placement." As described in the Prolift Surgical Technique Guide (2005) and the Prolift Surgeon's Resource Monograph (2007, which attaches the Technique Guide): "Perform a dissection of the entire thickness of the vaginal wall. It is preferred to leave Halban's fascia (pubocervical fascia) on the vaginal wall."

Prolift +M

In 2009, Prolift + M was introduced to the market. This device was identical to the original product in design except 1) the implant was replaced by Ultrapro, a composite mesh comprised of both non-absorbable Prolene and absorbable Polyglecaprone-25 monofilament (Monocryl); and 2) the posterior arms were angled differently. After absorption of the Monocryl product, the remaining Prolene was lighter in weight ($28g/m^{2)}$ compared to Gynemesh –PS ($45g/m^2$) without losing the strength of the original product. Some authors have suggested that lighter weight meshes have less deleterious effect on vaginal smooth muscle structure (Jallah Z. et al, The impact of prolapse mesh on vaginal smooth muscle structure and function, BJOG. 2016 Jun;123(7):1076-85, Feola A. et al, Varying degrees of nonlinear mechanical behavior arising from geometric differences of urogynecological meshes, J. Biomech. 2014 Aug 22;47(11):2584-9.)

There are several reports in the literature which demonstrate the safety and durability of Prolift +M. Milani et al. presented data on 128 women with stage 3 and higher prolapse who underwent the repair. At 3 years follow up, anatomical success was 75.9 %. Mesh exposure was observed in 19 subjects over 3 years (14.8 %) and no subjects had de novo pelvic pain. Resolution of pre-existing pelvic pain occurred in 7 (5.5 %) subjects. De novo dyspareunia was observed in 3/33 subjects (9 %). Khandwala (2013) presented 1 year data showing a composite success rate of 88.1%. There were 3 cases (2.2%) of vaginal mesh exposure. There were no visceral injuries. The incidence of de novo dyspareunia was 6%. Quemener (2012) reported their series of 250 patients who were followed a median of 20 months. The rate of re-interventions was 8%. The main indications were mesh exposure (2%), prolapse recurrence (1.2%), and stress urinary incontinence (4.8%). These authors compared their data with what was previously

obtained in their center with non- absorbable mesh. They found no difference in outcomes between the two procedures.

The findings in these studies reflect that Prolift +M is an effective device with an acceptable safety profile that is similar to Prolift. I have searched the medical literature and have not found randomized controlled trials demonstrating that Prolift +M is more effective or safer than Prolift, or vice versa.

The retrospective cohort trials comparing Prolift and Prolift +M reflect similar outcomes at one year postoperatively, including improved sexual health. (Lensen EJM et al., Comparison of two trocar-guided trans-vaginal mesh systems for repair of pelvic organ prolapse: a retrospective cohort study, Int'l Urogynecol. J. (2013); Bhatia N. et al., A comparison of sexual function outcomes 1 year after undergoing a transvaginal mesh procedure using polypropylene mesh vs. hybrid polypropylene/polglecaprone mesh (oral poster), Female Pelvic Med. & Recons. Surg, March/April 2012). In particular, Lensen et al. concluded: "Despite the considerable sample size of our study, no clinically relevant difference was demonstrated between the two groups of mesh." Although the authors reported some differences in exposure rates, they made clear that "it was impossible to know whether this was mainly due to the mesh properties or the increasing experience of the surgeons or a combination of both. Other complications and patients' overall improvements were similar."

Furthermore, these studies, in particular the Quenemer study, are consistent with my own experience with Prolift and Prolift +M. I used both products in approximately equal proportions in equal amounts over the 6 year period I was performing the procedure. There was little difference in the technical aspects – the dissection was the same as was the trocar placement and

tensioning. The Prolift +M had a heavier feel to it which made it lay flatter over the pelvic floor, but I never found the original product to be difficult to work with. I did not notice any differences in my success rates or in my mesh exposures (with the caveat that my exposure rates were negligible toward my last year of using the product, but this was more a function of my overall experience and had little to do with the material itself). Nor did I note any differences in patient satisfaction. Ultimately, whether to use Prolift or Prolift +M was a matter of surgeon preference.

FDA Public Health Notifications

The FDA first issued a safety communication regarding the use of mesh for pelvic reconstructive surgery in October 2008 and began collecting additional information on mesh complications through the MAUDE (Manufacturer and User Facility Device Experience) database. An FDA update was issued in July 2011, detailing their analysis of the reporting database (FDA Safety Communication: UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse. U.S. Food and Drug Administration (FDA). July 13, 2011). In the 3-year period between the 2 FDA communications, an additional 2874 mesh related complications were posted on the site. Although it was acknowledged that device reports typically increase after an FDA communication, the emphasis of the 2011 updated notification was that complications from transvaginal mesh used to repair POP are ''not rare.'' In the 2011 report, which focuses on TVM for POP, the FDA performed an independent literature review and concluded that TVM in the apical and posterior compartments does not provide substantial added benefit. Furthermore, this document asserted that although TVM in the anterior compartment may provide anatomic benefit, this does not necessarily result in improved symptomatic results. The statement does not

list the complications associated with traditional non-mesh repairs. However, it is important to note that in this document the FDA did not specifically recommend against the use of mesh for repair of POP, nor did the FDA identify any particular mesh or mesh kit.

Medical Society Statements

In response to the mass confusion and fear generated by the FDA warning and its subsequent medicolegal fallout, several well written responses to the FDA update have been issued by professional societies, including the American Urological Association (AUA), Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU), American Urogynecologic Society (AUGS), American College of Obstetricians and Gynecologists (ACOG), and Society of Gynecologic Surgeons (SGS). Most of the statements are in agreement with the FDA statement regarding surgeon training, proper selection of patients, detailed counseling of the patients about the treatment options as well as information regarding the complications related to mesh use, and the need for postmarket studies to confirm efficacy and safety.

In November of 2011, the AUA released a position statement on the use of vaginal mesh for the repair of pelvic organ prolapse. The statement acknowledged that:

> Many women undergo mesh POP repairs without complications. There is no convincing evidence that vaginal mesh placement can cause an autoimmune response, and there is no reason to remove vaginal mesh in asymptomatic patients. In patients who have had vaginal mesh surgery for pelvic organ prolapse and are satisfied with their results, there is no need to take any action other than routine check-ups and follow-up care.

ACOG and AUGS had similar views and issued their recommendations for the safe and effective use of vaginal mesh. These included:

- Standardization of subjective and objective success for all prolapse repairs and reporting of complications and reoperations
- Pelvic organ prolapse vaginal mesh repair should be reserved for high risk individuals
- Surgeons placing vaginal mesh should undergo training specific to each device and have experience with reconstructive surgical procedures and a thorough understanding of pelvic anatomy.
- Compared with existing mesh products and devices, new products should not be assumed to have equal or improved safety and efficacy unless clinical long-term data are available.
- Continued audit and review of outcomes, as well as the development of a registry for surveillance for all current and future vaginal mesh implants.
- Rigorous comparative effectiveness randomized trials of synthetic mesh and native tissue repair and long-term follow-up are ideal.
- Patients should provide their informed consent after reviewing the risks and benefits of the procedure, as well as discussing alternative repairs.

Furthermore, a joint statement by AUGS and ACOG in March of 2013, which addressed the problem of restriction of options for patients requiring pelvic floor reconstruction, stated:

> The 2012 Cochrane Review: Surgical Management of Pelvic Organ Prolapse concluded that "The use of mesh or graft inlays at the time of anterior vaginal repair reduces the risk of recurrent anterior wall prolapse on examination. Anterior vaginal polypropylene mesh also reduces awareness of prolapse however these benefits must be weighed against the increased operating time, blood loss, posterior or apical prolapse and reoperation rates for mesh exposures associated with the use of polypropylene mesh". A review of more current studies from 2011 and 2012 suggest that transvaginal mesh placed by experienced mesh surgeons may have mesh erosion rates comparable to abdominally placed mesh.
>
> There are certain clinical situations where many would agree the use of transvaginal mesh is not only acceptable, but preferred. Examples of these clinical situations include: patients with recurrent prolapse after a non-mesh, native tissue repair; or patients where an abdominal approach may pose additional and potentially more significant surgical risks like patients with pulmonary co-morbidities or patients with known significant intra-abdominal adhesions. It is our strong opinion, that there are subsets of women with prolapse, and in some cases those with the most advanced disease in whom the benefits

of transvaginal mesh outweigh the risks and a blanket ban on the use of these products compromises patient care.

Based on my personal experience, review of the medical literature, training, teaching, and interaction with colleagues, I strongly agree with these statements.

Material Properties

Plaintiffs' experts offer several opinions regarding so-called particle loss and fraying, degradation, chronic foreign body reaction, excessive contraction, roping, curling and other issues that they contend make Gynemesh PS and Ultrapro unsafe for use in Prolift. Regarding claims of "particle loss" and "fraying", there is no evidence in the medical literature whatsoever to suggest that this occurs in either Ultrapro (Prolift +M) or Gynemesh PS.

Furthermore, the overall extensive body of clinical data for Gynecare products employing Prolene (including Gynemesh PS, Prolift/+M and TVT brand products) does not support the conclusion that Prolene degrades in the body in any manner that has a clinical impact on patients. Clavé et al. (2010) studied how polypropylene mesh which was explanted due to erosion or infection was altered from its pre-implant state. The authors used histologic, chemical analysis, infrared spectroscopy and differential scanning calorimetry. Monofilament polypropylene products had less surface cracking (which they reported was degradation) than multifilament products. Clavé et al. noted that despite exhaustive testing, they could not explain their findings. They stated, "Several hypotheses concerning the degradation of the PP are described. None of these, particularly direct oxidation, could be confirmed in this study." The authors conceded that a weakness of the study was that there was no opportunity to compare explanted mesh from uncomplicated procedures with explanted mesh from the complicated procedures which makes it difficult to conclude if there would also be alterations in products which had not eroded or

become infected. Given these limitations recognized even by the study's authors, it cannot be concluded to a reasonable degree of medical certainty or probability that mesh degradation happens in a clinically significant way. This issue has also been evaluated by medical societies AUGS and SUFU which have concluded that the clinical data do not support the extrapolation of reported "surface cracking" in a minority of the Clave samples to degradation. (AUGS-SUFU Frequently Asked Questions by Providers: Mid-urethral slings for Stress Urinary Incontinence. March 2014).

Nor does the medical literature provide evidence that the use of Gynemesh PS results in excessive contraction of tissues causing complications to the patient in the absence of overtensioning or failure to ensure that the mesh is lying flat. To the contrary, Dietz et al. report that based upon ultrasound imaging, the polypropylene mesh does not contract or shorten over a median observation period of 1.6 years: "We found no evidence of mesh shrinkage beyond 3 months after implantation. Over an observation span of almost 60 woman-years, there was no evidence of a reduction in mesh diameters. On the contrary, midsagittal mesh length at rest and on Valsalva seems to have increased by almost 10% over a period of 18 months on average. If mesh contraction exists, it is unlikely to be a progressive phenomenon and is probably limited to the period of physiological wound healing." (Dietz, AJOG 2011).

There have been reports in the literature which have specifically addressed the issue of mesh contraction. Feiner and Maher (2010) performed a case series of seventeen patients who underwent surgical repair of vaginal mesh contraction at their institution. They defined contraction as "any abnormal findings such as focal or diffuse tenderness, increased mesh tension, or the presence of prominent bands under the vaginal mucosa." Ten of the patients had had their index operation at the same institution. The authors did not offer a definitive reason for

the finding of mesh contraction and acknowledged that it may have been a technical issue at the time of implant. This and other studies (Blandon, Hansen etc.) which looked at women who experienced a mesh complication did not provide an accurate overview of the true incidence of such a finding as there is no denominator to compare the number of patients who have not experienced symptomatic mesh contraction.

Large case series are far more informative on the incidence of such complications. (See Oxford pyramid of evidence.) de Landsheere et al. performed a retrospective 3 year study on 600 consecutive patients treated with Prolift from a single center. 524 patients were available for follow up and of those, only 2 patients (0.4%) experienced symptomatic retraction requiring wide mesh excision. A large systematic review by Schimpf et al. (2016) reported a return to the operating room for mesh related complications which would include erosion, exposure, contraction etc. of 3-8%. Thus, considering that the vast majority of patients in the literature do well with mesh repairs, it cannot be concluded that excessive contraction occurs with any degree of regularity.

Certain of plaintiffs' experts have pointed to notions of subclinical infection and foreign body reaction as a reason for mesh exposure and contraction. Neither of these conclusions have any basis in the literature on Gynemesh PS implants in the human body. Letouzey et al. studied PP mesh implants in rats and concluded that bacterial infection was responsible for decreased incorporation into tissue during the healing process resulting in mesh shrinkage. Other researchers have found a consistent but self-limited contraction rate of 3-20% of the initial surface area in the rat model (Sivaslioglu AA, et al., A randomized comparison of polypropylene mesh surgery with site specific surgery in the treatment of cystocele. Int Urogynecol J Pelvic Floor Dysfunct 19:467–471 (2008)). Nevertheless, in my vast review of the medical literature I

have encountered no studies which support the concept of subclinical infection or foreign body response as a reason for mesh complications in the human female undergoing a TVM procedure. On the contrary, Amid type 1 polypropylene mesh has decades of literature supporting its safety and efficacy in the human body. Any material implanted into the body will attract the attention of the immune system, but polypropylene mesh has proven itself to be the most compatible of materials we have used in female reconstruction to date. (Cosson, M. et al., Mechanical properties of synthetic implants used in the repair of prolapse and urinary incontinence in women: which is the ideal material? Int'l. Urogynecol. J. (2003) 14: 169–178).

Finally, in my experience of over 500 Prolift procedures, I have only seen a mesh curl in the human body when unnecessary amount of tension is placed on the implant causing it to deform. The Prolift IFU clearly states the importance of a tension free placement. Under warnings it stated "Do not remove the Gynecare Prolift cannulas from the patient until the mesh implant has been properly positioned." This is because the cannulas allow adjustment of the mesh. Once the cannulas are removed the arms are deployed in the tissues making further adjustment such as loosening difficult. The IFU further stated under precautions "Avoid placing excessive tension on the mesh implant during placement."

In my review of the medical literature, my interactions with colleagues, and in my surgical experience, I have not found evidence of an alternative device or mesh implant that reduces or eliminates the potential risks associated with Prolift or Prolift +M that are described above. For example, abdominal sacral colpopexy which is not an alternative device, but a procedure by which mesh is implanted through a different route, does not reduce the risks of prolapse surgery for women; it just changes them. Mesh exposure rates may be slightly lower (although there is data to suggest that experienced Prolift implanters had rates of exposure

comparable to ASC exposures) but, as discussed earlier in this report, other complications such as bowel obstruction and visceral injury are higher with intra abdominal procedures. Surgeons performing both this procedure and TVM have to be fully aware of the pelvic anatomy, dissection technique and material properties of the implant in order to perform the procedure safely and effectively.

Prolift/Prolift +M Warnings

The Prolift and Prolift +M IFUs and the Prolift professional education materials including the Prolift Surgeon's Resource Monograph and Surgical Technique Guide appropriately reflect the potential risks associated with the use of the devices as they are commonly known by pelvic surgeons and reported in the peer reviewed medical literature which I have researched and considered in preparing this report. This opinion is based on numerous factors:

1. The substantial medical literature that has studied Gynemesh PS, Prolift, and Prolift +M over the past 15 years, including Level 1 meta-analyses and randomized controlled trials, and prospective studies. My detailed review of that literature leads me to the conclusion that the Prolift and Prolift +M IFUs and professional education materials such as the Prolift Surgeon's Resource Monograph appropriately reflect the potential risks that are reported in the peer reviewed medical literature, and may appropriately omit risks that are commonly known or general surgical risks. I have also reviewed and considered the FDA's "Blue Book Memo" which provides guidance on device labeling, and Ethicon's Standard Operating Procedure on Labeling (HMESH_ETH_11642462), but these sources are not as important to me as the peer reviewed medical literature in assessing the potential risks of these products. While labeling

guidance documents from the FDA and the company provide general information on the goals of labeling, the medical literature provides detailed information on what adverse events have actually been demonstrated in thousands of women tracked over time, some of them for several years.

2. My extensive surgical experience in implanting approximately 500 Prolifts and 200 Gynemesh PS, as well as treating patients who were implanted by other doctors.

3. My years of experience in training residents and fellows in how to perform Gynemesh PS and Prolift/Prolift +M procedures. For the past 8 years I have been associate fellowship director of an ACGME- approved FPMRS fellowship program. For the years that Prolift and Prolift +M were available, I employed a systematic approach to teaching fellows to safely place those products by reviewing the instructions for use with them, having them watch me place them and ultimately supervising their performance in placing them on their own. This process equips me to evaluate the adequacy of the IFU because I have an understanding of what a new user needs to know in order to safely and effectively perform the procedure. I have periodically reviewed the IFUs for Prolift and Prolift +M with my fellows as part of their training on the devices.

4. My attendance at numerous medical conferences, including the Annual Meetings of medical societies such as AUGS and SUFU, where I have observed numerous presentations of Gynemesh PS, Prolift and Prolift +M data in the hands of many different surgeons who have presented their findings in oral presentations, posters and abstracts.

5. My training as a urology resident and as a Fellow in Female Urology and Voiding Dysfunction at the New York University School of Medicine, where I was trained to perform pelvic surgeries by Dr. Victor Nitti.

The Prolift and Prolift +M IFUs state indications, contraindications, surgical steps, warnings and precautions and adverse reactions associated with the use of those devices. The first bullet point of the original Prolift IFU Warnings and Precautions section provides that "Users should be familiar with surgical procedures and techniques involving pelvic floor repair and non-absorbable meshes before employing the Gynecare Prolift Pelvic Floor Repair System." (ETH.MESH.02341527). This language is very important because it conveys that Ethicon expects that the users of these devices will be trained pelvic floor surgeons with a base knowledge of pelvic floor anatomy and risks of pelvic floor surgery in general. That section further advises physicians to avoid large vessels, nerves, bladder and bowel, and that "attention to patient anatomy and correct use of the device will minimize risks." It also reinforces the instructions for the surgical placement of the device in emphasizing: "Avoid placing excessive tension on the mesh implant during handling." The Adverse Reactions section of the IFUs correctly reflects the potential complications that are reported in the most reliable medical literature --- meta-analyses, RCTs, and long and medium term prospective observational trials – which are discussed in detail above in my report. Those listed risks include injuries to organs, nerves and vessels associated with the implant surgery, infection potentiation, extrusion, erosion and scarring that results in contraction.

It is my opinion that because the vast body of medical literature does not demonstrate the cytotoxicity, degradation, chronic inflammation or chronic foreign body reaction leading to complications and other negative consequences that plaintiffs' experts allege, these claimed effects do not need to be warned about in the IFU.

I have also reviewed the 2009 revisions to the Prolift IFU note that while it used additional language and descriptions to describe potential risks, or re-stated the risks that were

previously warned about, it did not provide information that was new to the medical community. Much of the added language relates to general risks of pelvic floor surgery that are not a function of the device (for example, that there may be pelvic pain, pain with sexual intercourse, or urinary symptoms), or that are commonly known if not obvious to a trained pelvic floor surgeon. The references to pelvic pain, pain with intercourse and voiding dysfunction that were added to the Prolift IFU in 2009, for example, are both general risks of pelvic surgery, are commonly known by pelvic floor surgeons, and are reported in the published medical literature. These risks were specifically listed in the Prolift +M IFU from its launch. The Prolift professional education slide deck from 2007 also specifically address these complications, including reference to complications rates in the studies available at that time.

The Prolift Surgeon's Resource Monograph supplements the warnings discussions in the IFUs. It is a booklet that was issued by Ethicon starting in 2007 and compiles the advice and best practices of a panel of 10 surgeons who were experienced in Prolift at that time. It provides detailed guidance on patient selection and preparation, surgical technique, anesthesia and hydrodissection, incisions and additional sutures, mesh handling, technique pearls, comcomitant surgeries, and potential complications. In particular, the Monograph dedicates two full pages of discussion to the potential risks of "Erosion, Exposure and Extrusion" and "Dyspareunia and Vaginal Pain." It also provides a summary of clinical data that was available at the time of its publication, and attaches the Prolift Surgical Technique Guide that was issued in 2005.

In addition, I have reviewed Ethicon's patient brochures for the Prolift/Prolift +M. For the same reasons as discussed above with the IFUs and professional education materials, find them to be appropriate for the limited role of a patient brochure. They are comprehensive in their discussion of the disease state of prolapse, treatment options and potential risks. The risk

discussion mirrors the IFU and is not misleading. While the patient brochures do not list every possible risk that a patient could encounter in surgery, that is not the role of a patient brochure. Rather, it is the role of the patient's physician to engage the patient in a comprehensive risk discussion that is tailored to the patient's individual presentation and medical history.

Summary of Opinions

For the reasons set forth above, it is my opinion to a reasonable degree of medical certainty that:

1. Gynecare Gynemesh PS, Prolift and Prolift +M are safe and effective products that are supported by a substantial amount of clinical data, and are an appropriate treatment options for many women who suffered from the difficult and embarrassing condition of prolapse.

2. The benefits of Gynemesh PS, Prolift and Prolift +M outweigh their risks in a patient who is a proper candidate for surgery, and they are not defectively designed. My opinion on this is based on: 1) the performance of these products in these clinical studies which I have reviewed and which has been presented at conferences – Level 1 meta-analyses, RCTs and long term prospective studies studying thousands of women over several years; 2) my extensive surgical experience implanting these devices and treating women who have been implanted with them; 3) my interactions with colleagues; 4) my training; and 5) my instruction of other phyisicans .

3. The Gynemesh PS used in Prolift and the Ultrapro mesh used in Prolift +M are appropriate, effective and safe materials for use in this indication. Polypropylene mesh and sutures have been used an implant for decades. Based on my review of the peer-reviewed

medical literature and my surgical experience implanting these devices and treating patients who have had them implanted, the pore sizes of these meshes are appropriate.

4. The body of clinical data for Gynemesh PS, Prolift and Prolift +M does not support the conclusion that nonabsorbable Gynemesh PS degrades in the body in any manner that has a clinical impact on patients. If it did degrade in a clinically significant way, surgeons would see far lower levels of durability in their repairs, and that is certainly not something that I have seen in the peer reviewed medical literature or my clinical practice over many years.

5. There is no credible evidence in the medical literature of an alternative mesh material that, when used to treat prolapse, reduces or eliminates the potential risks of Gynemesh PS or Ultrapro.

6. A foreign body/inflammatory response is an expected and desired physiological outcome of the placement of any surgical implant. The peer reviewed medical literature I have reviewed does not support the notion that this response has any negative impact on clinical outcomes when Gynemesh PS, Prolift or Prolift +M are placed correctly.

7. Contraction is described in the literature but cannot be differentiated from the concept of over-tensioning which is clearly warned about in the product IFUs and the Prolift Surgeon's Resource Monograph which explicitly state that the mesh should lay in loosely.

8. The Instructions for Use, professional education materials, and patient brochures accurately reflect the risks of these products as they are reported in the medical literature and are consistent with my training and extensive surgical experience. The IFU and the professional education materials also appropriately take into account the base of common knowledge and

experience of physicians who are trained to perform pelvic surgery to treat prolapse, as is specifically stated in the IFUs.

Expert Rates

My work on this matter has been or will be billed as follows: $500 per hour for records review, preparation of Expert Reports, and consultation; $4000 per half day of deposition or trial testimony; and $7500 for full day of deposition or trial testimony.

Consulting with Ethicon

Based on Ethicon's records, I have preceptored about five events for Ethicon between 2008 and 2011, in which I trained other doctors in the safe and effective use of Prolift and TVT products. For my services, I was compensated a total of approximately $10,000.

Dated: January 12, 2017

NICOLE B. FLEISCHMANN, M.D.